ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 9 March-April, 1951 Number 2

A HYPOTHESIS ON THE PHYSIOCHEMICAL PATHOGENESIS OF HYPERSENSITIVITY STATES AND COLLAGENOUS DISEASES

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ALTHOUGH there are many explanations for the physiochemical pathogenesis of hypersensitivity diseases, recent information helps clarify the detailed steps involved. The historical observations can now be integrated into a comprehensible pattern. The conflicting and even divergent, interesting and informative views of the immunologist, endocrinologist, neurologist, the enzyme and pharmacological biochemists, can now be brought into focus to explain why beneficial results have followed variegated therapeutic procedures.

Following clinical experiences with various steroids, no ready and suitable explanation was found to account for the benefits seen in some hypersensitivity states and collagenous diseases. It is the purpose of this communication to present a hypothesis which will explain the physiochemical processes that cause the pathological changes seen in these diseases and the presentation of reported material that is essential to the support of such a thesis, as well as the mechanism of adaptation to these processes.

Almost a century has passed since Addison[3] proved that the adrenal cortex is essential to life. The present availability of the purified adrenocorticoids[76,113,164,166] has unfolded a new era in medicine. In evaluating the pharmacological effectiveness of such compounds, it is immediately apparent that epinephrine, acetylcholine and histamine are involved. The interrelationship of these three substances, along with the enzymes and adrenocorticoids, formulates the basis for this present hypothesis. This presentation does not furnish all the most minute physiochemical details but, in part, outlines the mechanisms involved. It may act as a guide to future studies.

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It must be emphasized that this abnormal mechanism seems to take place in only those who have an *inherited predisposition* to the development of hypersensitivity states and collagenous disease. It is our belief that in these individuals the tissues have an abnormal responsiveness by exhibiting exaggerated reactions toward acetylcholine and histamine formed in the sensitized end organs. Regardless of the precipitating factor or factors, the pathologic reaction and the attempt at adaptation occur in two phases. The catabolic phase concerns the deleterious effects produced in the tissues and is due to the incompletely antagonized acetylcholine and histamine. The anabolic phase involves the adrenal corticoids which enhance the formation of enzymes that inhibit or neutralize the excess of acetylcholine and histamine present.

CATABOLIC PHASE

Histamine.—Laboratory and clinical investigations agree that histamine is produced in the antigen-antibody reaction,[36,98,155] trauma,[21,28,39,138] infection[55] and "stress," including light, cold, heat[110,111] and emotions.[27] Histamine is a normal constituent of all tissues,[38,193] but especially the lungs, epidermis and liver. There is strong presumptive evidence that cellular injury, however produced, liberates histamine. The extent of the injury depends on the amount of histamine produced and the number of reacting histamine-sensitive cells in the body.

Patients with clinical hypersensitivity have a diminished tolerance to histamine.[163,203] Small amounts of histamine will precipitate typical reactions; e.g., bronchial asthma.

The pharmacological effects of histamine can be listed.[42,180] It is a parasympathomimetic-stimulating agent causing vasodilation, fall in blood pressure, increased capillary permeability, flushing of the face, sweating, salivation, rhinorrhea, lacrimation, and tachycardia. Other prominent effects include bronchiolar spasm with a sense of substernal constriction, increased intestinal peristalsis, and a rise in cerebrospinal fluid pressure. In man, small amounts cause a leukocytosis, eosinophiles predominating, followed by granulocytosis and lymphocytosis,[98] lasting from three to five hours.[126]

Animals subjected to prolonged histamine shock exhibit degenerative lesions in the aorta, the smaller arteries, and the myocardium; and focal fibroblastic proliferation in the spleen.[88] These peripheral responses to histamine, as well as to acetylcholine and epinephrine, are increased although the nerve supply has completely degenerated.[43]

There is no question that almost all of these peripheral pharmacological effects are seen in the patient suffering from a hypersensitivity state or a collagenous disease, whose organs or tissues exhibit the signs and symptoms of such reactivity.

The damaging effects produced are not due to histamine alone, as will be shown. They also stimulate the autonomic nervous system and hypothalamus, as illustrated (Fig. 1).

Hypothalamus.—The relationship of histamine to the autonomic system has long been known.[50] There is considerable evidence of the intimate relationship and control of the autonomic system by the hypothalamus,[15,16,149] stimulation of areas of which produces lesions in the gastrointestinal

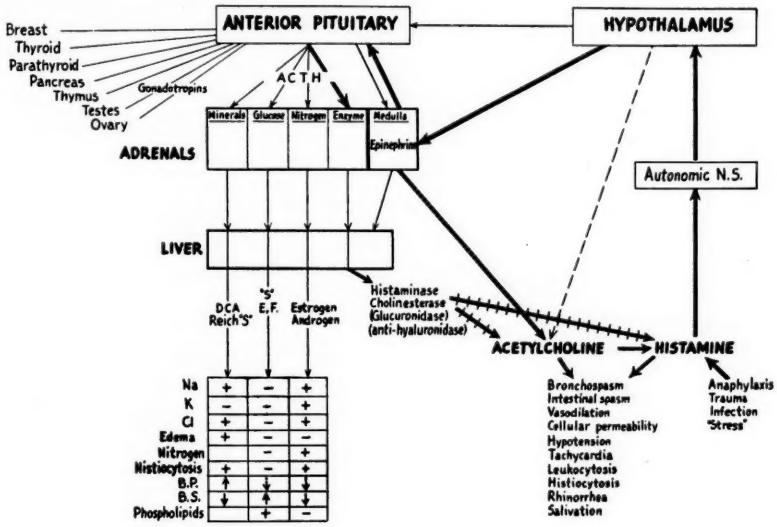

Fig. 1.

tract[32,33] which could be the result of formed acetylcholine or histamine. Allergic reactions to foods have been reported to cause similar lesions.[201]

The probability is that the peripheral deleterious effects are not produced directly by the hypothalamus but that the main effector mechanism is mediated through the adrenal medulla.[17,25,26,86]

Epinephrine.—Although acetylcholine and cholinesterase have been found in the adrenal medulla,[10] no abnormal amounts are released upon splanchnic stimulation.[79,112,139] The acetylcholine released serves only to stimulate the output of epinephrine.[53,80] Almost all of the epinephrine, so formed, causes an increased synthesis of acetylcholine in the peripheral tissues.[196] In denervated skeletal muscle epinephrine has been shown to potentiate the action of acetylcholine.[41]

Acetylcholine.—Patients with collagenous disease and hypersensitivity states show high blood levels of acetylcholine.[162] In status asthmaticus acetylcholine levels are extremely high, suggesting that there is a depletion of adrenal corticoids as well. In adrenalectomized animals acetylcholine

levels are increased,[90] and in the guinea pig heart a cholinergic substance is released during anaphylactic shock.[204]

Before the role of acetylcholine in the transmission of nerve impulses was elucidated,[107,108] its pharmacological effects on bodily tissues were

TABLE I. PHARMACOLOGICAL EFFECTS

	Histamine	Acetylcholine
Parasympath. stimulating	+	+
Vasodilation	+	+
Increased cellular permeability	+	+
Blood pressure	↓	↓
Tachycardia	+	+
Flushing of face	+	+
Perspiration	+	+
Salivation	+	+
Rhinorrhea	+	+
Lacrimation	+	+
Substernal constriction	+	+
Bronchiolar spasm	+	+
Intestinal spasm	+	+
Spinal fluid pressure	↑	↑
Leukocytosis	+	+

well known.[37,41,58,91] It is produced throughout the body.[34] Interestingly enough, the reported behavior of acetylcholine on the tissues locally is essentially similar to that of histamine (Table I). Large doses of acetylcholine produce pulmonary edema similar to that seen in anaphylactic shock[7] in animals; and, in humans, an intravenous injection is followed by a sensation of obstructed breathing leading both to increased rate and depth of respiration, a burning sensation in the throat and a desire to cough—all abolished by the administration of atropine.[29]

As with histamine, excessive administration of acetylcholine gradually causes a hyperplasia of the internal layers of the blood vessels as well as areas of focal necrosis in the myocardium, lungs and kidneys.[77] Acetylcholine also induces the release of histamine,[8] thus completing the catabolic cycle of events.

It is readily seen, therefore, that the pathology of hypersensitivity states and collagenous disease depends on the persistence of the unantagonized deleterious pharmacologic effects in the peripheral tissues not only of histamine but of acetylcholine as well.

ANABOLIC PHASE

After any type of stress the body mobilizes its forces to adapt itself to this stress.[176] Such an adaptation has been recognized as the "Universal Law," where any system that is in equilibrium tends to compensate in such a direction as to maintain this state.

The continuity between the catabolic and anabolic phases is maintained mainly through the stimulation of the anterior pituitary chiefly by means of epinephrine derived from the adrenal medulla and, to a lesser degree, directly from the hypophysis.[89] It is our belief that in nonsensitive individuals about equal amounts of epinephrine go to stimulate the anterior pituitary as go to cause the formation of acetylcholine and histamine. In hypersensitive individuals, through heredity, the balance is tipped more easily so that more epinephrine goes to form acetylcholine and histamine than in the direction which stimulates the anterior pituitary to release the adrenocorticotropic hormones. This is illustrated by the fact that 25 per cent of allergic patients had low 17-ketosteroid excretions, about 50 per cent of asthmatic patients had high potassium values, and one-third had low sodium and chloride blood levels.[52] It has been shown that the anterior pituitary nevertheless responds, although it is devoid of its nervous and vascular connections with the hypothalamus.[151]

Adrenal Cortex.—Because the adrenal cortex not only is vital in maintaining bodily equilibrium in normal states but also participates actively in the adaptation to trauma and acute disease, as manifested by a transient rise in 17-ketosteroid excretion, followed by a marked depression and then a gradual rise with convalescence,[57] research was instituted to isolate its active steroids. Those corticoids now available afford an opportunity to study their pharmacological effects. The release of adrenocorticotropic hormones is dependent on the reflex secretion, through the autonomic system, of epinephrine which directly activates the anterior pituitary and upon the rate of utilization of these hormones within the organism.[114,122] Dependent on metabolic requirements, epinephrine can act directly on the liver to cause gluconeogenesis by mobilizing glycogen stores.

In the adult, the adrenal gland consists of the following layers: a narrow outer zone (zona glomerulosa); a quite wide zona fasciculata; a narrower zona reticularis; and a large inner core, the medulla. In infancy, the medulla is thin and there is no zona reticularis, which develops about the third year. The latter anatomical fact may have a correlation with spontaneous remissions of hypersensitivity states having an onset in infancy. Apparently, the zona glomerulosa is not a "stress" zone, because it retains its size and ketosteroid content after stress or continuous administration of corticoids.[13,176,186] Following repeated injections of epinephrine there is hypertrophy and an increased ketosteroid content of the fascicular zone. The "alarm" reaction is characterized by a depletion of ketosteroids from the fascicular and reticular zones. These two inner zones also atrophy

following continuous administration of cortisone, but on discontinuation of therapy, there is a return to the normal state. In "exhaustion" it is in these two zones that there is a decrease in the ascorbic acid content of those cells which normally contain this substance diffusely.

Clinical research permits us to assume that there are four functional groups of adrenocortical activities, each having its own distinctive characteristics: the mineralocorticoids, the glucocorticoids or "S" hormones, the nitrogen or "N" hormones, and an amorphous group of steroids which require further clarification.

Mineralocorticoids.—These steroids are exemplified by desoxycorticosterone and desoxycortisone (Reichstein's compound "S"). They are so named because they are concerned with and act in the presence of mineral ions. They are characterized by an absence of oxygen on carbon atom 11. When desoxycorticosterone is administered there is a retention of sodium and chlorides and a loss of potassium, predisposing to a retention of water in the tissues.[60,175] This compound has a profound stimulating effect upon the proliferation of fibroblasts and collagen formation.[115,189] Desoxycorticosterone produces a hypertension[136] and a hypoglycemia.[179]

It has been confirmed that desoxycortisone (Reichstein's compound "S")[118,174] is a mineralocorticoid and had the same effects as desoxycorticosterone,[150,175,177,178,213] producing widespread connective tissue proliferation, salt retention, edema, blood pressure rise, hyalinization of glomeruli, interstitial myocarditis, and panarteritis; the lesions characteristic of hypertensive, rheumatic and allergic conditions in man. Adrenalectomized animals develop these lesions more readily after treatment with these steroids.[178]

Desoxycorticosterone potentiates the effect of epinephrine.[144] Peripheral damage due, therefore, to acetylcholine and histamine can be accentuated in the presence of adrenocortical imbalance when a preponderance of mineralocorticoids is being secreted.

Glucocorticoids.—These steroids are characterized by having an essential oxygen on the carbon atom 11. Typical examples are cortisone (Compound E) and Compound F. They are chiefly concerned with increased gluconeogenesis from the breakdown of amino acids and opposing the action of insulin[49,99,192] with a consequent rise in blood sugar and glycosuria. The glucocorticoids, in part, serve to antagonize the effects of the mineralocorticoids[49,60,115,136,175,189,192] by lowering sodium and chloride levels, retaining potassium slightly and producing a diuresis (combating some of the edema present). The hypertension produced by desoxycorticosterone is abolished by cortisone.[136]

The effect of the glucocorticoids on nitrogen metabolism is a mixed blessing. Although they depress production and cause lysis of the fibroblastic and collagenous tissues,[49,115,140,189,192] they increase urinary nitrogen

excretion, causing a marked negative nitrogen balance. Cortisone suppresses all elements in wound healing.[87,181] This marked inhibition and lysis of protein elements of the body by the glucocorticoids does not help explain the beneficial clinical effects in hypersensitivity states seen following their administration. One group of investigators[153,205] feels that these corticoids lead to an increase of circulating antibodies through the involution of lymphoid tissue. However, the preponderance of evidence shows that the glucocorticoids have no demonstrable effect in increasing the circulating antibodies[63,78] and, as a matter of fact, there is an actual suppression of antibody formation.[56,63,187] Cortisone does not prevent anaphylactic hypersensitivity reactions, nor does it prevent the Arthus reaction,[56] although it does temporarily inhibit the delayed tuberculin reaction in sensitized animals, probably due to its inhibition of the histiocytic and lymphocytic responses.[187,214] It is through this latter mechanism that the glucocorticoids prevent hypersensitivity lesions produced in animals after being produced by the mineralocorticoids,[19] since no lymphocytes are available to form antibodies.

In addition to the above effects, the glucocorticoids cause a mobilization of cholesterol and increased turnover of liver phospholipids.[4,5,99,109,135] Liver function is improved generally[202] occurring in hypophysectomized animals[64] although abolished by adrenalectomy.[70,109,135]

"N" Corticoids.—These steroids resemble the structure of the mineralocorticoids more closely than the glucocorticoids because of the lack of oxygen at carbon atom 11 and are best represented by the sex steroids: androsterone, estrone and progesterone. Their peripheral actions represent an admixture of the effects seen with the mineralocorticoids and the glucocorticoids. The sex steroids predominate in their influence on nitrogen metabolism, resulting in anabolic effects[100,152,173] illustrated by an increase in serum albumin.[161] Androgens enhance potassium retention[49] and cause a disappearance of ascites and edema, although cirrhosis of the liver may be present.[161] Testosterone causes a lowering of the blood pressure in postmenopausal patients,[119] reducing, as well, the blood sugar levels, cholesterol levels and insulin requirements of diabetic individuals.[24] Similar results are obtained with estrogens in animals[92] and in humans.[207]

Although testosterone stimulates histiocytes and the formation of intercellular ground substance,[117] massive doses have been reported to benefit chronic arthritis; this amelioration is also produced by progesterone.[48]

In reviewing the data to this point, it is readily concluded that none of the adrenal cortical steroids, alone or together, account for a specific antagonism of the peripheral damage seen in collagenous and hypersensitivity diseases. If all of these corticoids are secreted simultaneously, as they probably are, then the sum of all these effects almost amounts to neutrality. The glucocorticoids almost completely antagonize the mineralocorticoids, and the sex steroids almost completely inhibit the remaining unantagonized

actions of both. Therefore, another group of anabolic cortical steroids must be considered.

Enzyme Corticoids.—It is our belief that these steroids comprise an amorphous group concerned with oxidation-reduction reactions within the tissues and involve specific enzymes, vitamins and melanins. These steroids also act through the liver, as well as directly on the peripheral tissues. When exogenous cortisone is given, it causes its own direct pharmacologic effects and, through a rebound reflex, it depresses the anterior pituitary in secreting ACTH which releases the enzyme corticoids along with the others. When ACTH is given there is not the marked antibody suppression as seen with cortisone alone.[63] Cortisone added directly, *in vitro,* to blood of rabbits sensitized to sheep erythrocytes has no effect on the release of histamine when the blood is mixed with the sheep cells.[30] Therefore, the glucocorticoids do not antagonize histamine, but other adrenal corticoids, or enzymes, are produced in the intact animal which mitigate the damaging actions of acetylcholine and histamine in the peripheral tissues and favorably influence the course of the abnormal state.

Adrenalectomized animals are more vulnerable to anaphylactic shock, and such animals are more sensitive to histamine.[14,137,216] In these there is a rise in the histamine content of the tissues, and histamine tends to disappear more slowly from the blood as well as from the tissues.[158,159] In rats, adrenalectomy also causes a fall in the histaminase content of the tissues which can be reversed by adequate doses of adrenocortical extract.[96,156]

The release of adrenocorticotropic hormones in response to intravenous histamine is very rapid (within five seconds).[65] Asthmatic and rheumatoid patients treated with ACTH excrete decreased quantities of histamine[84,157] and do experience relief.[147] The clinical relief noted was undoubtedly due in major part to the specific destruction of histamine in the tissues by production of the enzyme, histaminase. There is no question that the histamine is quantitatively destroyed by histaminase.[9,20,217,218]

Histaminase.—Histaminase is found abundantly in the lungs, kidneys, spleen, muscles, adrenals and in the blood. The liver contains surprisingly little. The placenta contains a great deal, and in pregnancy there is an enormous increase in the blood level, reaching a peak at the seventh to eighth months. Histamine levels, however, are about the same in the nonpregnant as in the pregnant woman.[95]

Clinicians are quite familiar with the spontaneous remissions of asthma, allergic dermatitis and rheumatoid arthritis during pregnancy when chorionic gonadotropin titers are high. As a matter of fact, this thesis was promulgated in order to explain the mechanism whereby "Marisone,"* comprising mixed natural steroids, estrogen free, derived from pregnant mares' urine (to be reported separately) and a chorionic gonadotropin

*See footnote, page 141.

preparation, "A.P.L."®* relieved asthmatic patients. Although the vital capacity did not increase, a patient in early status asthmaticus who exhibited difficulties during the luteal phase of her menses was relieved of dyspnea. There was a marked diminution of pulmonary râles in twenty minutes after the parenteral administration of 4000 I.U. of the chorionic gonadotropin. Further investigations are progressing to determine whether adrenocorticotropic hormones were thus released through the anterior pituitary, producing a rise in tissue histaminase and cholinesterase, or whether the preparation contained any ACTH besides the LH factors.

In any event, however, histaminase is not the only agent which destroys histamine.[160]

Cholinesterase.—The enzyme cholinesterase is widely distributed throughout the body. It accelerates the destruction of acetylcholine.[6,120] These may not be primarily responsible for neural conduction alone.[103]

Although serum and blood cholinesterase levels vary between individuals, species, diets, liver function and seasons,[106,116,154] in humans the levels are significant and fairly constant.[124] A review of the literature reveals that there are two types of cholinesterase,[11] specific and nonspecific.[12] By means of a special staining technique,[101] it was confirmed that specific cholinesterase is predominantly limited in activity to striated muscle, preganglionic fibers, smooth muscles of the bronchioles and urinary bladder, the effector cells of the parotid gland and erythrocytes. The nonspecific cholinesterase was found almost exclusively in the sensory ganglia, hepatic cells, adrenal cortex, plasma, carotid body and the longitudinal muscles of the ileum. In the remaining autonomic ganglia, adrenal-medulla and in blood vessels both types of cholinesterase were present. It is also noted that the outermost portion of the zona glomerulosa stained for nonspecific cholinesterase activity. It will be recalled that this is the adrenal zone that shows no change following stimulation with mineralocorticoids and glucocorticoids. Apparently the zona glomerulosa is the most stable area of the adrenal cortex. Changes due to stress are not as obvious in this adrenal zone because enzyme metabolism occurs in peripheral tissues to a greater degree than in the adrenal cortex itself and in contrast to the participation of the sex steroids, mineralocorticoids and glucocorticoids acting from the adrenal cortex itself.

Cholinesterase exists in concentrations four to ten times in excess of physiological requirements,[102,121] and 50 to 80 per cent or more of the enzyme must be destroyed or inhibited before the effects of anticholinesterase drugs are detectable.[128] Marked inactivation of nonspecific cholinesterase sensitizes the organism to small doses of acetylcholine.[81]

It must be emphasized that even though normal blood cholinesterase values can be found during the active allergic state, it does not minimize

*Kindly provided by Ayerst, McKenna & Harrison, Ltd., New York, New York.

the fact that the patient is reacting because of a hereditary hypersensitivity to acetylcholine. Too much stress should not be placed on venous blood cholinesterase values.[71,85] What is most significant is the process which takes place in the peripheral tissue. It is believed that subjects with collagenous disease and hypersensitivity states are more susceptible to normal amounts of acetylcholine than are nonsensitive persons.

A recent publication[142] considers the administration of cholinesterase, intravenously, as a specific for the therapy of hypersensitivity diseases. The enzyme is well tolerated and apparently without any serious toxic effects.

Although cholinesterase and histaminase account for the major portion of the inhibition of peripheral damage, there are two other enzymes which must be considered, antihyaluronidase and glucuronidase, since they also influence the tissues involved in the tissue pathology seen in hypersensitivity and collagenous diseases.

The mucopolysaccharide hyaluronic acid is an important constituent of the intercellular ground substance of connective tissue and is probably formed by the fibroblasts. Normal serum contains a nonspecific inhibitor of hyaluronidase.[45,68] Adrenalectomy and the administration of desoxycorticosterone[131,211] augment the effect of hyaluronidase on connective tissue and allow for the easier spreading of damaging agents through tissues. The increase of adrenal corticoids induced by epinephrine or ACTH decreases the activity of hyaluronidase in the skin of humans.[170,185] However, inactivation by the adrenal steroids of hyaluronidase does not occur *in vitro*.[132] This would imply that antihyaluronidase is not formed in the adrenals but is produced in the liver upon stimulation from the adrenal corticoids. In all of the *in vivo* corticoid experiments the liver was left intact. It has been reported that the adrenal corticosteroids such as cortisone, testosterone[132,210,211] and the related steroids[171,172] have marked inhibitory effects on hyaluronidase. These actions can be measured almost quantitatively.[168] Since the glucocorticoids have been shown to suppress all elements in wound healing, this effect is probably also due to antihyaluronidase activity[181] as well as to the antagonizing of the histiocytic response due to the mineralocorticoids. It may be inferred that the peripheral connective tissue hyperplasia following administration of the mineralocorticoids is mediated through the augmented secretion of hyaluronidase or by means of the mitigation of antihyaluronidase.

Glucuronic acid, which is synthesized in the liver and muscle directly from glycogen or the sugars resulting from protein breakdown, also plays a role[143] in the normal development and maintenance of all connective tissue. An increase in glucuronic acid is seen in systemic intoxication and in chronic diseases.[212] It probably helps oxidize tissue toxins which are neutralized by forming conjugates with glucuronic acid.[83] The activity of glucuronic acid depends on its enzyme, glucuronidase, which is also predominantly formed in the liver.

DISCUSSION

In consideration of the foregoing facts, other diseases of unknown etiology may be grouped with the hypersensitivity and collagenous diseases. The physiological observations lead to the hypothesis of a common and fundamental basic relationship.

Certain of the muscular dystrophies may be of allergic origin. Total cholinesterase levels fall preceding exacerbations of multiple sclerosis.[94] Dystrophy patients show marked thickening and proliferation of the media and adventitia layers of blood vessels, and occasionally complete obliteration of the lumen. Large doses of desoxycorticosterone can produce periodic paralysis in dogs.[54] Spasms of muscles, especially of the nuchal group, have been proven to be the result of an allergic reaction in humans.[146] There is less dysarthria, spasticity and reduction in the hyperactivity of deep reflexes in muscular dystrophies following adrenocorticoid therapy.[148,184] This clinical finding is not accompanied by a marked change in cholinesterase levels, but it is thought that the improvement is due to a better retention of potassium which acts as a potentiator of acetylcholine[129,130,184,194] in its effect on the effector organ. Epinephrine also causes increased cell permeability to potassium. Potassium is known to increase the responsiveness of muscle tissue to an effector stimulus. Yet, in some tissues, the corticoids must inhibit acetylcholine synthesis to account for the striking alleviation of pain and euphoria seen after cortisone therapy[184] so that pain impulses are not transmitted.

Myasthesia gravis, although characterized by a type of neuromuscular dysfunction, is probably not of allergic origin but due to a dyscrasia within the adrenal cortex or the pituitary, producing excessive enzymes which result in an alteration in the threshold response[208] or an excessively rapid destruction of acetylcholine.[40] In this disease, it is noted that eserine helps and that potassium intensifies the action of eserine.[195] When the adrenal corticoids are given, the patients become worse and only improve after the cessation of such therapy.[73] The exogenous corticoids cause a temporary suppression in the endogenous adrenal enzyme-stimulating corticoids. After ACTH or cortisone therapy a slight fall in cholinesterase level has been noted.[123]

In view of the hereditary patterns and the favorable effect of certain steroids, one is tempted to classify neoplastic disease as the result of a hypersensitivity state. It is conceivable to us that cells become hypersensitive to unantagonized acetylcholine and histamine; and as a result of this chronic tissue "poisoning," there is an abnormal metabolism and growth pattern of cells in an attempt to adapt themselves to the immediate toxic environment produced in the sensitized organ tissue. Once this process has begun these cells are refractory to the normal concentrations of the physiological inhibitors. Encouraging results have been obtained with massive doses of the "N" steroids (sex steroids)[2,59,72,125,188,202] and enzyme preparations,[52,62,67,141] especially in the treatment of prostatic, mammary and

lymphatic malignancies and in certain leukemias. The benefits after glucocorticoid therapy have been also reported.[82,133,134,190] Removal of the adrenals increases the incidence of lymphatic leukemia[127] in susceptible rats. In tumor-bearing animals the total amount of adrenal steroids is much below normal, except cholesterol.[22]

At present, there is no clear-cut explanation as to the mechanism of the beneficial effects following the administration of exogenous corticoids. Some of the published generalizations are in agreement with the present hypothesis. All seem to agree that, "The great diversity and apparent nonspecificity of the action of adrenal steroids suggest some single fundamental action at the cellular level . . . an action on cell permeability may well prove to be a common denominator of their ubiquitous effects. One proved mechanism involved in this reaction is the demonstrated ability of these hormones to inhibit the formation of histamine following the union of antigen and antibody and accelerate its breakdown."[191] Others feel that in addition to the interference with substances produced in the antigen-antibody reaction there is an alteration of responsiveness of the mesenchymal tissues[66,206] and a change in cell permeability due to the action of the hormones on hyaluronidase.[165] It is felt that the hypothesis of the fundamental physiochemical pathogenesis herein presented is compatible with all the foregoing theories but goes further in explaining the mechanism in greater detail as it occurs in the catabolic as well as the anabolic phases of collagenous and hypersensitivity diseases. It explains why the presence of two different types of histamine, intracellular and extracellular, need not be postulated,[35] but simply two agents, acetylcholine and histamine, which have similar peripheral effects. This theorem explains also why a large variety of agents have offered some relief in these clinical categories, which may serve as additional proof that the acetylcholine and histamine are principally involved in producing tissue damage.

It is known that when histamine or drugs such as prostigmine or mecholyl, simulating acetylcholine or inhibition of the cholinesterase, are given, the disease is aggravated or precipitated; e.g., asthma. Antihistaminic agents have effectively controlled a large percentage of patients with hypersensitivity reactions. These agents antagonize acetylcholine as well,[31,93] but weakly when compared to their specific antihistamine action. This would account for the incomplete effectiveness of such compounds, especially in those patients with a marked sensitivity to acetylcholine or where more acetylcholine remains uninhibited than histamine. What is needed is an agent which is an efficient inhibitor or antagonist to acetylcholine as well as histamine to treat hypersensitivity states and collagenous disease.

Some have reported excellent clinical results with histaminase but others disagree.[145] As has been pointed out, an incomplete result might be expected with such a regimen. Cholinesterase alone would give better results, as indicated, because when acetylcholine synthesis is inhibited then the production of histamine is inhibited also.

Large doses of epinephrine have given relief in allergic reactions as well as in arthritis. This is readily explained by the specific pharmacologic effect of epinephrine in relaxing smooth muscle as well as through the augmented secretion of the adrenal enzyme corticoids.

The inconsistent relief seen with testosterone, estrone and progesterone in the treatment of hypersensitivity states depends on the physiological state of the adrenals and can act as endogenous corticoids. Their effectiveness is limited by adrenocortical hypofunction and involution, which increases with age[104,105] or exhaustion. It is a common clinical notation that the elderly are more difficult to treat with the same methods effective in the younger group. The frequency of collagenous disease and the higher incidence of intractable hypersensitivity states in the elderly is undoubtedly related to the hypofunction of the adrenal cortex, with a consequent lowering of cholinesterase and histaminase levels in the tissues. Estrogenic hormones and pregnenolone have been discovered to increase the synthesis of acetylcholine while most other steroid hormones decrease the amount synthesized.[197]

Authorities agree[76,97] that the glucocorticoids merely alleviate symptoms and reverse certain signs temporarily but cannot be considered as curative. They do not cause long-lasting benefit, since they do not give rise to any protective antibody release.[69]

Ephedrine is useful because it has an anti-amine-oxidase action preserving epinephrine which goes on to release pituitary adrenocortical hormones.[1]

Barbiturates have been used empirically for many years in the treatment of collagenous diseases and hypersensitivity states. Barbituric acid competes with thiamine and inhibits the synthesis of acetylcholine[44,198]; so that less acetylcholine is produced.

Vitamins, which are intimately related to the metabolism of enzymes, vary in their abilities to enhance acetylcholine synthesis. Vitamin C, vitamin E and most members of the B group increase the amount of acetylcholine synthesized; while vitamins A, K and D decrease the synthesis.[198] These vitamins do not have a direct and specific action but act nonspecifically through other cell processes. In general, it is inferred that the enzyme involved in the synthesis of acetylcholine contains an active SH group, since the process is inhibited by agents that decrease the activity of the sulfhydryl group (unsaturated ketones, oxidizing agents, alloxan) and is increased by agents protecting the activity of this group (antioxidants, glutathione and cysteine).[18,200,210]

Antibiotics have been helpful probably because they also inhibit acetylcholine synthesis; e.g., penicillin.[199]

Atropine has been used for many years with good results in bronchial asthma. It does, however, cause a marked inspissation of mucus in the lungs. Atropine prevents the access of acetylcholine to the cells of organs innervated by the parasympathetic nervous system. It has been shown that atropine is active against both acetylcholine and histamine.[167]

Procaine and cocaine have been attended by beneficial results in bronchial asthma and in arthritis[61] and other hypersensitivity diseases.[169] It has been found that many local anesthetics have antiacetylcholine as well as antihistamine properties.[16] Incidentally, the ethylenediamine and piperazine antihistaminic compounds are also fair local anesthetics and many have definite atropine effects (muscarinic anticholinergic action). This same relationship is seen with quinine and quinidine compounds. However, procaine is relatively safe for intravenous use and is rapidly destroyed in the liver. Some analgesics, antihistamines and quinidine were found to inhibit not only acetylcholine but epinephrine and histamine as well.[47]

Finally, we know that the state of pregnancy and lactation increases resistance to histamine shock,[183] and often dramatic remissions of hypersensitivity and rheumatoid diseases occur during this time.[74,75]

MANAGEMENT

In spite of all the foregoing, no radical or basic change can be recommended in the management of hypersensitivity states or collagenous diseases. The empirical methods of the past, though clinically proven, now have a more scientific basis. It is still important to:

1. Prevent the antigen-antibody reaction and its subsequent train of events leading to tissue damage by eliminating the offending allergen or by hyposensitization. These measures bring more permanent benefits than any others. It has been proven that hyposensitized patients have more thermostable protecting antibody and, therefore, less histamine (and acetylcholine) is released compared to nontreated individuals.[182]
2. Infections should be promptly controlled since they result in cellular trauma which releases histamine.
3. Vigorous attention should be paid toward all measures that maintain good general and mental health to avoid other stresses. Sex hormones and vitamins should be given when so indicated.
4. A stable, nonpyrogenic, cholinesterase preparation can be given intravenously alone or in conjunction with antihistamines, epinephrine, procaine, ephedrine, atropine or barbiturates, according to habit, custom or choice.

SUMMARY

The present hypothesis stresses the fact that the peripheral tissue damage of hypersensitivity and collagenous disease is due principally to the pharmacological actions of insufficiently antagonized or an inherent hypersensitivity to acetylcholine and histamine, which augment the effects of each other. We find agreement[23] in this concept that, through epinephrine, acetylcholine and histamine act as local hormones and govern tissue activity in many organs.

The simultaneous anabolic processes in the body are stimulated and mediated through the anterior pituitary and to the adrenal cortex which

secretes steroids that produce enzymes, acting peripherally and inhibiting acetylcholine and histamine synthesis, thus preventing further damage to the tissues. Other hormones, such as ACTH, are useful only in that they stimulate the secretion of the beneficial enzyme-producing corticoids.

Consideration is given to a large variety of agents that have been shown to be of clinical benefit. It will be seen that amelioration of symptoms and signs produced by these agents is in proportion to their ability to act as acetylcholine and histamine antagonists.

CONCLUSIONS

1. The physiochemical pathogenesis of hypersensitivity and collagenous diseases is based on the imbalance between the catabolic phase, which produces tissue damage due to acetylcholine and histamine, and the anabolic phase, which concerns the secretion of enzyme-forming steroids from the adrenal cortex.

2. A collation and integration of the extensive research results of independent and reliable investigators support this hypothesis.

3. The efficacy of a large variety of therapeutic agents depends upon their ability to antagonize the pharmacological effects of acetylcholine and histamine in the tissues.

4. The best management of these diseases includes elimination of the offending allergen, hyposensitization, and the use of cholinesterase or other efficient antiacetylcholine and antihistaminic drugs.

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UNLABELED ALLERGENIC CONSTITUENTS OF COMMERCIAL FOODS AND DRUGS

A Critique of the Food, Drug and Cosmetic Act

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THE etiologic role of specific foods in causing various allergic syndromes is well established. In the absence of satisfactory nonspecific measures in dealing with the problems of food allergy and the consequent necessity of a specific approach, it is essential that physicians in this field are acquainted with the sources in the diet of the common allergenic foods. This knowledge is not only a necessary prerequisite for the diagnosis of specific food sensitivity by means of the direct technique of the individual food test[25,32,37] or as a result of elimination diets[39] but it is also an essential requirement in the treatment of the diagnosed patient.

In dealing with the highly sensitive patient, one learns that no amount of the specific food in question is too small to be regarded as insignificant.[37] For instance, the small amount of malted cereal extract contained as an unlabeled flavoring in a widely distributed brand of chocolate bar has resulted in the production of unmistakable allergic symptoms in six wheat-sensitive patients. The ingestion of identical candy bars except for the absence of the cereal extract failed to produce symptoms in the same individuals. In all instances the bars were fed under experimental conditions, that is, the patient did not know in advance which candy bar contained the cereal extract.

Other patients highly sensitive to black pepper have suffered acute allergic episodes following the trial ingestion of various commercial products labeled as containing "spices." The unsuspecting patient had no way of knowing outside of a severe symptom reaction that the spices in a given preparation included black pepper. On several occasions the identity of the spice was confirmed on inquiry of the manufacturer.

Unlabeled sources of corn sugar (dextrose or glucose) in canned fruits and preserves have been responsible for precipitating many acute reactions in highly corn-sensitive individuals.

Other instances have been observed in which the ingestion of the small amount of cornstarch encountered as an excipient in pharmaceutical tablets has resulted in the production of acute allergic reactions in corn-sensitive patients otherwise avoiding the sources of corn. In others the continued use of prepared foods containing corn sugar or the continued medication with drugs compounded with cornstarch has resulted in the perpetuation of the symptoms of masked food allergy[31] from corn exposure even though all other known sources of maize and its products were rigidly excluded from the diet. In such cases, otherwise completely

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diagnosed, the exclusion of such corn-containing preparations resulted in the amelioration of distressing symptoms. The test feeding of the processed foods or drugs in question resulted in a sharp recurrence of symptoms although there was no evidence of specific sensitivity existing to other ingredients of these same preparations.

These are not rare examples, each is chosen because it is representative of a particular type of problem; such experiences are encountered frequently in the practice of allergy if detailed efforts are made to diagnose specific food sensitivity by means of direct diagnostic techniques. In these instances, the unfortunate allergic consumer had no knowledge that the commercial product in question contained a food source which he was rigidly attempting to avoid. The inclusion of wheat, black pepper and corn respectively in these products entering interstate commerce was not in violation of any existing federal regulations, for these foodstuffs were included in the said products without the necessity of specific label declaration.

Experiences of this type prompt a criticism of the current standards of the Food, Drug and Cosmetic Act from the standpoint of the problem of the allergist and with the aim of affording a greater degree of protection for the allergic consumer. Certainly, if specific labeling is to be meaningful, the diagnosed allergic individual should be able to read the labels of his foods and proprietary drugs and thus be able to avoid recurrences of acute illnesses associated with the ingestion of his specific allergens.

THE FOOD, DRUG AND COSMETIC ACT OF 1938

Foods

The current Food, Drug and Cosmetic Act was approved by the president in mid-1938. This legislation superseded the Food and Drug Act of 1906, differing from it principally by the establishment of legal procedures for the formulation of definitions and standards for foods. The machinery by means of which such standards are adopted is as follows: The initiative may be taken by representatives of the Food and Drug Administration, by state regulatory officials, by the manufacturers of processed foods or by the consumers. A tentative definition and standard are published in the *Federal Register* in connection with the announcement of a public hearing at which all interests are given an opportunity for expression of their views. The submitted evidence is appraised, and in the event of a positive action the promulgated definition and standard for the product or products considered are announced in the *Federal Register*.

Many of the currently existing federal standards for foods were thus promulgated without an active medical interest in allergy or the point of view of the allergic consumer having been brought to bear in the public hearings. As a consequence, many standards permit the admix-

ture of important allergenic foodstuffs without the stipulation of such on the label of the processed product.

As space does not permit a review of individual food standards, and as the points to be raised are usually common to several different standards, the specific points of criticism will be named, the various standards to which these points apply will be listed, and finally, the clinical evidence in support of the stand taken will be cited.

This review has been facilitated by the recent publication in the *Federal Register*[12] of all currently effective definitions and standards for foods promulgated under the Federal Food, Drug and Cosmetic Act of June 25, 1938. Any reference to amendments subsequent to the date of this publication, October 30, 1948, will be mentioned specifically.

Spices, Natural Food Flavorings and Seasonings.—The provision of including various spices in standardized foods under the label designation of "Spiced," "Spice Added," or "With Added Spice" and the inclusion of natural food flavorings under the general terms of "Flavored," "Flavoring Added" or "With Added Flavoring" is deplored on the ground that the label does not indicate the presence of specific foods. Should an individual happen to be highly allergic to a particular spice or common flavoring, and having no knowledge of the presence of such from reading a label couched in general terms, he would have to depend upon the production of symptoms following the ingestion of the product in order to identify the presence of the allergen. Furthermore, in many instances, there is no clear designation as to the inclusiveness of the terms, "spices and natural food flavorings and seasonings."

The various standards which permit the nonspecific labeling of spices include: all cacao products except plain cacao (cocoa nibs or cracked cocoa), alimentary pastes, canned fruit except fruit cocktail, fruit preserves and jellies, fruit butter, canned peas, all other canned vegetables except canned beans, catsup, tomato paste and canned tomatoes.

Allergic reactions to spices are by no means rare and involve all the major condiments.[36,40]

The natural food flavorings in respect to cacao products include such diverse allergenic items as any natural food flavoring, oil, oleoresin or extract and, more specifically in respect to the sweetened chocolate preparations: ground vanilla beans, ground coffee, ground nut meats, honey, molasses, brown sugar, maple sugar, and dried malted cereal extract. Other standards permitting natural food flavorings without label declaration of the specific agents used are: canned peaches, canned apricots, canned pears, canned cherries, fruit jelly, canned peas, catsup, tomato paste and canned tomatoes.

All the permissible specific natural flavoring agents in chocolate have been incriminated as allergens. The same statement might be made for the fruit flavors.

The term, "seasoned with vinegar," is frequently used in standards without designation as to the origin of the vinegar. Unless labeled specifically the consumer might not know whether a given product contained apple vinegar, grape vinegar, malt vinegar or some other kind. This applies particularly to the specifications for canned peaches, canned apricots, canned pears, canned cherries, and all canned vegetables other than those specifically regulated (namely canned peas and beans). Vinegar, unspecified as to kind, lemon juice or lime juice may also be added to fruit preserves, jellies and fruit butter without the label bearing any designation as to the presence of these products.

Vinegars have been observed to be allergenic in respect to the source materials from which they are prepared.

Artificial Flavorings and Colorings.—Artificial flavors under the terms, "Artificially Flavored," "Artificial Flavoring Added" or "With Artificial Flavoring" may be included in all standards for sweetened chocolate. The cherries in canned fruit cocktail may be artificially flavored without the label bearing even this general designation.

Artificial color is a permissible addition to cherries in canned fruit cocktail but does not require label declaration; it may be added to fruit jelly with the label designation of "Artificial Coloring Added" or "With Added Artificial Coloring;" it may be employed in oleomargarine with the designation of "Artificially Colored," "Artificial Coloring Added" or "With Added Artificial Coloring" and finally it may be contained in certain substandard quality canned peas with the label designation of "Artificially Colored."

Although the artificial flavors and colors have not been specifically incriminated as a cause of allergic symptoms, it is of interest that Baer, Leider and Mayer[2] have shown that many patients sensitive to paraphenylenediamine show cross sensitization to certain azo dyes commonly used as food colors. Even though Calvery[7] was unable to produce sensitization in guinea pigs with these food dyes, Mayer[20] has pointed out such dyes may act as "eliciters" in the patient sensitized to related dyestuffs and in that sense may prove to be as dangerous as the sensitizers themselves.

The possibility of allergic reactions to the carriers or diluents employed in connection with artificial flavors and colors should be kept in mind.

Emulsifiers and Stabilizers.—Lecithin, usually derived from soy beans, may be added to certain food standards under the designation of "Emulsifier Added" or "With Added Emulsifier" without any label indication that the product contains a soy bean ingredient. This pertains to the regulations for sweetened chocolate preparations and oleomargarine.

Gelatin may be added to cream cheese and Neufchatel cheese with the

designation of "Gelatin Added" or "With Added Gelatin" without designation whether the gelatin was derived from porcine or bovine sources.

Similarly, vegetable gums may also be added to cream cheese and Neufchatel cheese under the designation of "Vegetable Gum Added" or "With Added Vegetable Gum" but without the specific gums being indicated on the label.

Pectin may be added to fruit jelly of various types without the label indicating its presence in the product. Commercial pectin is usually derived from apples or citrus fruit.

Commercial gelatin derived from beef and available as a food has been found to exert a specific allergenic effect in patients highly sensitive to beef.[21]

Gum karaya, one of the permissible vegetable gums employed in the manufacture of cream cheese and Neufchatel cheese is well known for its allergenicity as shown by the observations of Bullen,[6] Feinberg,[15] Bowen,[4] and Figley.[17]

Gum tragacanth, an optional ingredient employed similarly, has also been incriminated from the allergic standpoint by Gelfand[18] and by Brown and Crepea.[5]

Although carob bean gum has not been described as an allergen in humans, it is of interest that carob (St. John's wort or Hypericum) is a photosensitizing substance for animals.[42]

Sugars.—The permissible admixture of sugar of cane or beet origin (sucrose) with sugar of corn origin (dextrose or corn syrup) without labeling the source materials is the most troublesome deficiency of the currently effective federal food standards. All standards which permit the addition of sugar simply define it as sucrose without indicating whether or not it is prepared from cane or beets; these include the regulations for sweetened chocolate, sweetened condensd milk, canned peaches, canned apricots, canned pears, canned cherries, canned fruit cocktail, fruit preserves and jellies, fruit butter, canned peas, canned vegetables other than those specially regulated, and catsup.

The meaning of the term "dextrose" is not clear as it is defined variously in different standards. In the regulations for canned fruit cocktail, fruit preserves and jellies and fruit butter, dextrose is referred to as refined anhydrous or hydrated dextrose made from any starch; this conceivably might mean the starch of various fruits, corn or other cereals, potato, sweet potato, tapioca or other sources. In some standards, namely those for canned peaches, canned apricots, canned pears, and canned cherries, dextrose is defined as the hydrated or anhydrous refined monosaccharide obtained from hydrolyzed starch. Unless otherwise indicated, the term "starch" usually indicates cornstarch; at least this is the interpretation placed upon that word by the pharmacopoeia and by

common usage. In the regulations for sweetened chocolate preparations, dextrose means the anhydrous refined monosaccharide obtained from hydrolyzed starch. One standard, that of canned peas, permits the use of dextrose but does not define it. Finally, in the standards for sweetened condensed milk, canned vegetables other than those specifically regulated and catsup, dextrose is referred to as a synonym of refined corn sugar. The latter use of the term is obviously different from the first definition, in which an attempt is made to differentiate dextrose derived from any starch from dextrose derived from cornstarch, or the second usage, which attempts to differentiate dextrose from hydrolyzed starch versus corn syrup or the third which differentiates dextrose as an anhydrous preparation derived from starch from dried corn syrup.

One can see no conceivable advantage from this apparent play on words but there would be considerable advantage accruing to the consumer who happened to be highly allergic to corn if the presence of sugar derived from corn was clearly stated on the labels of commercial products containing it. This ideal is approached completely, however, in only one standard, i.e., the regulations for condensed milks which contain corn syrup. It is partially approached in the standard for fruit butter in that the presence of corn syrup or honey must be declared on the label but the presence of dextrose (almost always derived from corn) need not be so stated!

Sensitivity to cane sugar, first recognized by Duke,[10] (Case 23) and by Coca,[8] is being recognized by the writer with increasing frequency since it has been suspected as a cause of symptoms in all otherwise undiagnosed cases of food allergy.

Sensitivity to beet sugar, also apparently first described by Duke[10] and confirmed by Coca,[8] has also been diagnosed by Rinkel[34] and by Zindler.[46] Although it appears to be most common in areas where beet sugar is employed as the major source of sweetening, it is being encountered with increasing frequency in other areas. In the author's experience the ingestion or intravenous injection of refined cane sugar and the ingestion of refined beet sugar have caused unmistakable allergic reactions when administered under the experimental conditions of the individual food test.[25,32]

The allergenicity of corn sugar was first suggested by Urbach and Willheim.[43] Rinkel[33,35] emphasized the importance of avoiding sugar of corn origin (dextrose and glucose) in controlling the allergic symptoms of the corn-sensitive individual, a point also mentioned by Coca.[8] However, Ratner and Gruehl[30] claimed that corn sugar syrup and crystalline sugar derived from the hydrolysis of cornstarch were non-anaphylactogenic for guinea pigs, and presumably from this evidence concluded that these products were not important in clinical allergy. Randolph and Yeager[28] confirmed their animal work but disagree with their conclu-

sions in respect to the significance of corn sugar in clinical allergy. We have demonstrated that at least in certain highly corn-sensitive patients the ingestion of U.S.P. dextrose derived from the hydrolysis of cornstarch will cause unmistakable allergic symptoms. These findings are in keeping with the current views of Rinkel and Zeller.[37] In more recent data,[29] the intravenous injection of dextrose or glucose in the commercial form prepared for this use will also cause reactive symptoms in the corn-sensitive individual.

The importance of these observations cannot be dismissed in view of the fact that corn sensitivity is at least equal in incidence to that of wheat sensitivity as the major cause of food allergy.[37] In the writer's private practice corn sensitivity is diagnosed in approximately 40 per cent of individuals investigated for specific food sensitivity.[27]

Available information indicates that the specific designation of cane or beet sugar has not been heretofore regarded as an important point in the labeling of processed foods. Dextrose has been considered in a similar light since a ruling of the Department of Agriculture, December 26, 1930, which reads as follows: "Corn sugar (dextrose) when sold in packages must be labeled as such; when sold in bulk must be labeled as such; but the use of pure refined corn sugar as an ingredient in the packing, preparation or processing of any article of food in which sugar is a recognized element need not be declared upon the label of any such product." The definitions and standards of foods effective at that time were then revised in conformity with this decision; this policy has continued to the present time.

As a consequence of the failure to designate the type of sugar employed in various commercial products, it is necessary to warn the cane, beet or corn-sensitive individual to avoid all commercial sweetened foods except those known to be free of particular specific sugars, based on the statement of the manufacturer or as a result of test feedings in known specifically sensitized allergic patients. In view of the general tendency of food processors to use first one type of sugar and then another, one cannot be certain in the absence of any specific designation, that a product shown to be satisfactory for a patient at one time will necessarily remain free of the specific sugar to which the individual is allergic.

The absence of specific labels on commercially processed foods indicating the presence of corn products is the single greatest criticism of the current food standards, in that the failure to indicate the sources of corn causes more difficulty for the allergist who is diagnosing his cases of corn sensitivity correctly than any other single point mentioned in this presentation.

Oils and Fats.—The standards for enriched flour, enriched self-rising flour and enriched bromated flour permit the addition of vitamin D without stating the source of the material. The critical reader wonders if this

permits the addition of fish oils or vitamin D refined from such natural sources.

Oils and fats of various origins may be included in the standard for oleomargarine with the general designations of: "Prepared from Animal Fat" or "Made from Animal Fat"; "Vegetable," "Prepared from Vegetable Fat" or "Made from Vegetable Fat" or various combinations of these terms without the specific designation of the animal and vegetable sources.

Edible vegetable oils may also be added to canned artichokes and pimentos without the necessity of specific labeling as to the source of the oils.

As a general rule, the oil fractions of foods are less allergenic than other fractions.[37] Nevertheless, refined vegetable oils have been known to carry sufficient allergenicity as to cause symptoms when ingested by certain highly sensitized patients. It is granted that the incidence of such reactions is relatively infrequent. Duke[11] pointed out this relationship with soy bean oil. Rowe[38] has incriminated cottonseed, corn, peanut and olive oils. Although there was considerable debate in the recent hearings on salad dressings as to whether cottonseed oil is allergenic for the cottonseed-sensitive patient, the writer is in agreement with Rowe that cottonseed oil will cause symptoms in certain patients, having two cases under observation in which this has been demonstrated repeatedly as a result of individual food tests with the refined oil.[26] Corn oil is an unmistakable cause of symptoms in certain, but not all, corn-sensitive individuals. Peanut oil has been observed as a cause of symptoms both by ingestion and injection.

It is a common occurrence for the fats of mammalian foods to cause allergic symptoms when ingested by sensitized individuals; this is particularly true of pork.[44]

Fish oils have been incriminated as causes of allergic symptoms by Balyeat and Bowen[3] and Feinberg[14] in 1934 and confirmed by Hoffman and Rattner.[19]

Miscellaneous Carriers.—The standards for enriched farina, enriched corn meals, enriched corn grits, enriched macaroni products and enriched noodle products permit the use of "harmless carriers" which do not impair the enriched products, such carriers being used only in the quantity reasonably necessary to effect an intimate and uniform distribution of the thiamin, riboflavin, niacin or nicotinamide, iron and vitamin D in the finished enriched product. A statement of fact concerning the identity and sources of these so-called "harmless carriers" would be desirable.

Dried irradiated yeast may be employed as a source of vitamin D in these same standards. One wonders if cornstarch may also be included as "a harmless carrier" in the case of yeast in view of the practice of manufacturers of yeast to sell their product in cakes containing cornstarch; this

obviously would be of importance only in connection with the above wheat containing products.

In the most recent amendment to the standards for cereal flours and related products, published in the *Federal Register* of November 27, 1948,[13] dealing with the definitions and standards of identity of flour, enriched flour, bromated flour, enriched bromated flour, self-rising flour, enriched self-rising flour, and phosphated flour, the bleaching agent nitrogen trichloride (the agene process) is surplanted by the use of the following bleaching agents: oxides of nitrogen, chlorine, nitrosyl chloride, chlorine dioxide and benzyl peroxide. Of particular interest in this connection is the fact that benzyl peroxide may be mixed with various inorganic carriers and starch. Although the total amounts of such substances should not exceed six parts of weight to one part by weight of benzyl peroxide, the important fact remains that these recently promulgated standards permit the mixture of cornstarch with flour, enriched flour, bromated flour, enriched bromated flour, self-rising flour, enriched self-rising flour and phosphated flour without the label of the said flours indicating the presence of added cornstarch.

Allergy to the ingestion of yeast was described by Taub[40] and confirmed by Feinberg and Little.[16]

The allergenicity of cornstarch in the corn-sensitive patient is well established; this subject has recently been reviewed by the writer.[22,24]

Other Points.—It should be apparent to one familiar with the Food, Drug and Cosmetic Act and its currently effective amendments and food standards, that not all these regulations are discussed in this survey. Those not designated are satisfactory from the standpoint that they do not permit unlabeled extraneous food sources.

Another point, recently described and not considered in any of the current standards, is the question of a food being contaminated with other foods as a result of contact with the packing material. A raw or processed food having a moist or liquid phase in contact with a starched carton surface may and commonly does absorb starch from the container. The ingestion of such a food, as milk or cottage cheese, dispensed in carton containers has been shown to result in the precipitation of symptoms in corn-sensitive individuals who are avoiding other sources of corn exposure.[22] Starch may be absorbed from a container surface under such circumstances in spite of the type of waxing which is employed. There is a similar corn contamination from the interior surfaces of certain frozen food containers and from the common practice of dusting the inner surfaces of plastic wrappers employed in packaging certain brands of cheese.[22] The presence of starch on the inner surfaces of these wrappers may readily be demonstrated by performing an iodine test for starch on the interiors of such paper or plastic cartons.

Drugs

The major points of criticism of the Food, Drug and Cosmetic Act in respect to the labeling of drugs pertain to the permissible use of various excipients, diluents and encapsulating agents without the necessity of the labels declaring their presence. This legislation is apparently interested only in the active pharmaceutical ingredients of medications and carries no stipulation as to the label listing of these so-called "inert ingredients," many of which are important food allergens.

Food Sources Employed as Excipients, Diluents and Encapsulating Agents.—Cornstarch is the most important food used in this connection, being employed as an excipient in the majority of tablets designed for ingestion and also as a diluent in many powders and capsules.

The first instance of the allergenicity of cornstarch employed as an excipient was reported by Rinkel[33] in 1944. The first case proved by the author was reported in 1948.[23] Since this time several other instances have been observed.[24] In the highly corn-sensitive patient, otherwise avoiding sources of exposure to corn, the small amount of cornstarch in a tablet of desiccated thyroid or aspirin is sufficient to cause a sharp recurrence of the symptoms of corn sensitivity. The continued use of tablet medication containing cornstarch has resulted in the perpetuation of the chronic symptoms of masked corn sensitivity; these were not relieved until all sources of maize were excluded from the diet.

The allergenicity of corn sugar employed as a diluent in a cough sirup was also observed by Rinkel.[35] Chronic coughing resulting from sensitivity to corn, did not subside until the proprietary cough remedy was discontinued. Glucose sirup, employed as a substitute for simple sirup in prescriptions, and the use of corn sugar as a sweetening agent in lozenges have been incriminated by the writer[24] as causes of symptoms in corn-sensitive individuals.

The injection of codeine prepared from tablets containing lactose as an excipient has been found responsible for precipitating localized reactions at the point of injection and constitutional symptoms in highly milk sensitive individuals whereas the same dosage of codeine prepared from pure crystals has been tolerated in the absence of such responses.[24]

The use of gum tragacanth as an excipient has been reported by Brown and Crepea[5] as a cause of allergic symptoms. Although gum acacia and gum karaya are sometimes employed as excipients, they have not been reported as causing symptoms when employed in this capacity.

The use of sucrose, derived from cane and from beet sugar, has been found to produce allergic symptoms when taken in the form of diluents in prescriptions by specifically sensitized allergic individuals. This practice of employing sucrose in medications without a label statement as to the source of the material is an occasional cause of unexplained symptoms.

The use of gelatin and other agents in encapsulating pharmaceutical

preparations may prove to be a cause of symptoms in allergic individuals specifically sensitized to the agents employed.

According to the current regulations, there is no stipulation concerning the labeling of liver extract preparations as to whether the source material may have been beef or pork liver. Neither has the Food and Drug Administration required the specific labeling of the oil or wax used in penicillin preparations although this practice is recommended by the United States Pharmacopoeia. The same statement might be made in connection with other official preparations in oil and in respect to many nonofficial pharmaceuticals in which nonaqueous vehicles are employed.

The problem presented by the use of food in pharmaceutical preparations has been judged of sufficient importance to induce one firm to produce a line of medications free of the major allergenic excipients.† This point of view, of particular importance in connection with the newer antihistaminic drugs, is receiving increasing attention. At the present time the majority of antihistaminic drugs still contain such allergenic excipients and diluents as cornstarch, lactose, gum tragacanth and others. The manufacturers of Hydryllin, Histadyl and Pyrollazote have prepared these products free of the more common food excipients. It is to be hoped that other pharmaceutical firms will do likewise.

DISCUSSION

It should be emphasized that this criticism pertains primarily to the terms and provisions of the Food, Drug and Cosmetic Act of 1938 and not to the administration of that act. It is generally agreed that considering the difficulties inherent in regulating the manufacture and sale of commercially prepared foods and drugs that the current legislation has been fairly administered. We do not wish to give the impression that, as physicians, we are not grateful for the degree of protection afforded the consumer under the terms of the current act, including the labeling provisions as they are currently interpreted. The purpose of this communication is to point out the need for detailed regulation pertaining to the more explicit labeling of so-called optional food ingredients now permitted in processed foods and drugs, the labeling of which is either not required or permitted to be stated in nonspecific terms.

It should be further stressed that the officer in charge of hearings in respect to the proposed standardization of a particular food is guided solely by the evidence presented at such hearings. Neither the hearing officer nor the administrator should be criticized if the allergist's point of view, as expressed herewith, has not been brought to bear at hearings held prior to the promulgation of certain particular standards. As these standards of identity are based solely on facts submitted as evidence, it behooves the allergists as individuals or as representatives of their organizations to see that their point of view is submitted at future hearings, at the possible

†Prepared by the Upjohn Company under the trade name, "Abergic."

reopening of past hearings and, particularly, if and when the Food, Drug and Cosmetic Act of 1938 is amended or otherwise modified.

It should also be realized that the formulation of definitions and standards of identity for various foods under the provisions of the current act represents a departure in the activities of the Food and Drug Administration concerning which increasing experience has been acquired during the past decade and about which there has been considerable debate and some controversy from the standpoint of various other interests. For reviews of this subject the reader is referred to recent articles by Austern[1] and Crawford.[9]

Of the various groups affected by the enactment of such standards, in the past the food processors and manufacturers have been most vocal in expressing their point of view at the preliminary hearings. The protection of the consumer's interest has rested principally with the officials of the Food Administration, in the absence of organizations representing the voice of the consuming public.

Not only have the allergists failed to bring their point of view into the hearings and other activities of the Food and Drug Administration, but there has not been any other sustained medical interest in these important questions having such a direct bearing on the nutrition of the nation other than that shown by the Council on Foods and Nutrition of the American Medical Association and that of the nutritionists as recently stated by Wilder.[45] There is need for a greater medical and public health concern in respect to this subject than has heretofore been displayed. This represents a challenge to the medical profession and to those engaged in public health work who logically should be the consumer's spokesmen in such matters.

Returning to the position of the allergist, his motivating desire in this connection is that he and his patient may read the label of a processed food or drug and determine the ingredients contained therein. Although it is freely admitted by all that the enactment of the Food, Drug and Cosmetic Act was designed to protect the general consumer and has been administered with that point of view foremost, the fact remains that many of the current regulations are deficient in affording the desired degree of protection to the allergic consumer. Although a given standard may specifically define and list the various foodstuffs which may be included in the product, the patient reading the label of the package is commonly at a loss to know what foods actually were added to the specimen at hand. This criticism is particularly pertinent to the standards for sweet chocolate and catsup but it also applies to varying degrees to many other food standardizations and the drug regulations pertaining to excipients and diluents.

The allergist and his patients have no objection to the existence of a certain number of such food combinations which make for greater palatability or add other desirable characteristics if the package is labeled as to the

precise food constituents contained therein. However, the tremendous increase in the number of such commercially prepared food conglomerations in recent years is alarming to the physician interested in the practical handling of the problems of food allergy, for it has resulted in a marked increase in the incidence with which certain foods commonly employed in such compounding practices are actually ingested. The current importance of corn sensitivity, for instance, is judged to be the direct result of this practice, for it is known that the incidence of food allergy to particular articles of the diet is proportional to the frequency with which such foods are used in the diet.[37]

Rinkel[36] has pointed out the desirability of employing a rotating and diversified diet in the prophylaxis and control of food allergy, a point of view endorsed by the writer. Prophylactically, the food allergy process is less apt to develop if an individual eats a wide variety of foods and avoids the oft-repeated use of any food. Therapeutically, the diagnosed patient minimizes the possibility of a spread of the sensitization process if he rotates the use of the various tolerated primary foods and avoids the cumulative use of any article of the diet. Although this dietary plan may be put into effect in the home where foods are individually prepared, it is becoming increasingly difficult to follow this type of diet under any other circumstances in view of the increasing tendency to mix major foods. Although we cannot expect the Food and Drug Administration to reverse this current trend in merchandising, it does not seem to be an unreasonable request to ask for the specific labeling of the food constituents of processed foods and drugs.

SUMMARY

The Food, Drug and Cosmetic Act of 1938 is criticized on the basis that many of the definitions and standards of identity of foods promulgated under the provisions of that act permit the addition of various allergenic food ingredients to standardized foods without indicating their presence on the labels of the products. The perpetuation of this practice has been a cause of considerable inconvenience to practicing allergists and the unexplained cause of symptoms in individuals who happen to be highly sensitive to the foods in question.

Similarly, other foodstuffs may be added to medicinal preparations in the guise of excipients, diluents and encapsulating agents without their presence being indicated on the labels of the processed drugs.

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HYPERSENSITIVITY STATES AND COLLAGENOUS DISEASES

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HERPES GESTATIONIS

Case Report

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HERPES gestationis is a member of a small group of eruptive, vesicular, and bullous dermatoses which resemble each other morphologically. Others considered in this group by Sulzberger[2] are: herpes simplex and zoster, dermatitis herpetiformis (Duhring's disease), pemphigus, and erythema multiforme. In some of these, the underlying etiology and pathogenesis are obscure, and the management, therefore, remains nonspecific.

Mueller and Lapp[1] collected fifteen cases of herpes gestationis in their review of the literature for the ten-year period, 1934 to 1944, and added two of their own. This suggests the relative rarity of this dermatosis or the infrequency with which the diagnosis is made and confirmed.

Likewise, in the case that is to be presented, the diagnosis was not originally apparent nor precisely established until adequate observation was possible and only after the differential diagnosis had been thoroughly explored.

In the case to be reviewed, the diagnosis rested chiefly between herpes gestationis, dermatitis herpetiformis, and erythema multiforme. Obviously, it was important to rule out pemphigus. Herpes simplex and zoster were not seriously considered as possible diagnoses.

Briefly, some of the pertinent differential diagnostic criteria are as follows:*

A. Herpes gestationis:
   1. Onset usually in the second half of pregnancy in periumbilical area.
   2. Alternating exacerbations and remissions with acute flare-up following delivery and ultimate recovery.
   3. Possible recurrences with repeated pregnancies.
   4. Eosinophilia as high as 50 per cent.
   5. High incidence of stillbirths, spontaneous abortions, and deformities.
   6. Morphologically characteristic eruption of dermatitis herpetiformis.

B. Dermatitis herpetiformis:
   1. Relatively uncommon, cause unknown.
   2. Pruritic, burning, polymorphous eruption—characteristic lesion is a vesicle.
   3. Symmetrical distribution.
   4. Chronic course with frequent remissions.
   5. Eosinophilia.
   6. Possible exacerbation on exposure to halogens with positive inunction patch tests with potassium iodide.

Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

*The author expresses his thanks to Dr. H. Woolhandler, University of Pittsburgh, Department of Dermatology, who assisted in the preparation of the data on differential diagnosis.

7. Hyperpigmentation of the involved area.
8. Fair general health.

C. Erythema multiforme:
1. Frequent mucosal lesions, oral and genital.
2. Pruritus not so severe as in dermatitis herpetiformis.
3. Characteristic lesions—target-like; vesicles may or may not be present.
4. No characteristic eosinophilia.
5. Not subject to frequent recurrences and remissions; occasional seasonal remissions in spring and fall, attacks lasting two weeks.
6. Occasionally accompanied by severe toxicity.
7. To be differentiated from drug and toxic eruptions.
8. Possible manifestation of bacterial allergy.

D. Pemphigus:
1. Cause unknown, rare, often fatal.
2. Characteristic lesion—bulla rising on normal skin.
3. Asymmetrical distribution.
4. Pruritus slight or absent.
5. Toxicity apparent.
6. Treatment nonspecific.

From time to time, the following case presented some of the aspects of each of the vesicular dermatoses noted above, which necessitated its consideration in the differential diagnosis.

CASE REPORT

Mrs. E. G., white, twenty-five years of age, in her seventh month of pregnancy, developed an itching and burning eruption in the periumbilical area. Soon after, similar lesions appeared on her thighs. These were described as intensely pruritic blisters on inflamed and burning areas of the skin. They remained essentially unchanged until the day following the termination of the pregnancy.

Because of a rising blood pressure, labor had been induced two weeks prior to the estimated date of confinement with the following technique—the administration of castor oil followed by artificial rupture of the membranes. Labor was present for eleven hours. Under gas anesthesia, the patient was delivered of a normal baby girl.

On the following day, the patient was distressed with generalized intolerable pruritus involving the palms of the hands, soles of the feet, and even the toenails and the fingernails. Erythematous blotches appeared in discrete and confluent patches on the abdomen, breasts, thighs, calves, and arms. These persisted with superimposed vesicles of various sizes. A phenol-containing lotion was applied which caused secondary irritation. In ten days the patient was discharged from the hospital. After her return home the lesions increased in number and the vesicles increased in size.

I was asked to see her four days later. She presented a picture as described. Immediate rehospitalization was advised, and she was admitted to the Montefiore Hospital, Pittsburgh, Pennsylvania.

Past Medical History.—She claimed that she had not felt well since her first pregnancy two years ago. During that pregnancy, she had gained 30 pounds and developed hypertension and generalized edema in the last trimester. That pregnancy was likewise terminated by the induction of labor. Thereafter, she had been suffering constantly from chronic backache and pelvic pain; this was attributed to uterine retroversion.

The second and last pregnancy had progressed normally with a weight gain of only seventeen pounds. She had been placed on thyroid gland extract therapy from the fourth to the ninth months, inclusive. She reported her basal metabolic rate as minus 5 per cent. Her usual weight ranged between 160 to 170 pounds. Other medication taken consisted of daily iron and vitamins (multicebrin). She stated that she had taken no other drugs, tonics, laxatives, medications, or iodized salt.

During her childhood, she had had measles, scarlet fever, and pneumonia. Tonsillectomy and adenoidectomy were done at the age of five. A pilonidal cyst was removed in 1938.

Associated Allergies.—Perennial allergic rhinitis of several years' duration; occasional urticaria; nausea after codeine sulphate and the sulfonamides. (My impression was that this was probably idiosyncrasy and not true drug allergy.)

Family History.—Her father has ragweed hay fever and bronchial asthma; a sister has chronic rhinitis; a sister has chronic urticaria. Her mother is living and well except for menopausal symptoms. One son, two years of age, is apparently well. Her husband is living and well.

Symptoms Referable to the Various Systems.—Essentially negative except for the following: Obesity had been present since fourteen years of age. Dyspnea was noted on exertion. She possessed a very nervous temperament, and observed exacerbations of the pruritus with emotional upsets.

Physical Examination.—This patient was a young, white, moderately obese, two weeks' postpartum woman. She was in apparent great distress, bordering on hysteria, complaining bitterly of itching, burning, and pain in the involved areas of the skin.

*Skin.**—There was an eruption covering chiefly the arms, forearms, thighs, legs, and feet, including a few lesions of the soles, and to a lesser degree also the abdomen and chest. It consisted of pinhead to pea-sized vesicles and larger bullae. There were patches of coin-sized to large palm-sized erythematous and circinate areas with some tendency to central clearing. Some of the *vesicular lesions arose on clear, unaffected skin,* while *others were located on the erythematous patches.* On a few sites there was a faint yellowish-brown hyperpigmentation. There were no lesions in the mouth or the other mucous membranes. On puncture, some of the vesicles contained as much as 2 cubic centimeters of serosanguineous fluid.

The physical examination was otherwise essentially negative.

Laboratory Findings

Blister Fluid.—Culture—negative; smear—75 per cent polymorphonuclear leukocytes, 25 per cent eosinophiles.

Blood Chemistry.—Sugar—93 milligrams per cent; nonprotein nitrogen—32 milligrams per cent; inorganic phosphate—3.7, and calcium—12.7 milligrams per cent.

Blood Counts.—Hemoglobin—13.5 grams; red blood corpuscles—4.8 million; white blood corpuscles—varied between 6800 to 12,750, polymorphonuclear leukocytes—from 49 per cent to 65 per cent, lymphocytes—from 25 per cent to 31 per cent, eosinophiles reported as 3, 12, 14, and 23 per cent.

Sedimentation Rates.—Varied with the progression of the dermatosis from 47 millimeters to 14 millimeters in one hour (Cutler method).

*See Figures 1A and 1B.

Basal Metabolic Rate.—Before thyroid therapy was minus 32 per cent; last report was minus 6 per cent.

Urine.—Routine, negative; negative for sulfa crystals and porphyrins.

Fig. 1A *(above)* Forearm. Note vesicles and bullae superimposed on an erythematous base.

Fig. 1B *(below)* Thigh. Note similar lesions as in Figure 1A.

X-Rays.—Chest-calcified Ghon's complex in right hemithorax; no active pulmonary disease. Heart—upper limits of normal size and configuration. Teeth—several small cavities revealed.

Electrocardiogram.—Within normal limits.

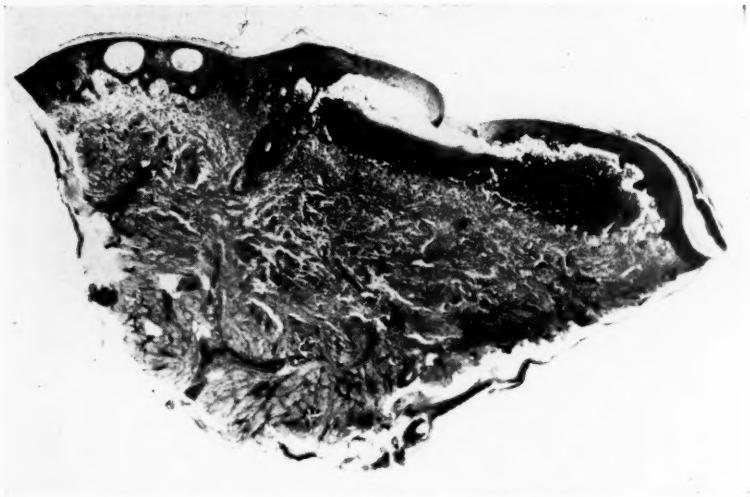

Fig. 2. Biopsy section. Note subepidermic bulba and multiple intraepidermic vesicles.

Inunction and Patch Tests.—These were performed on unaffected and previously affected sites with 50 per cent potassium iodide in petrolatum ointment. Patch tests were positive at forty-eight hours, with a three to four plus vesicular response on the previously affected site, and an erythematous and vesicular response on the unaffected sites. (Performed by Dr. Rudolf L. Baer, New York City.)

Biopsy Section. (Fig. 2)—The horny layer is deep and lamellous. Three-quarters of the section shows a subepidermic bulla. The epidermis covering the bulla shows a rather normal structure with some exocytosis. Within the bulla are found nuclear debris besides a great number of polys among which no eosinophiles can be found. Small intraepidermic vesicles filled with fibrin, and some polys and nuclear debris are to be seen apart from the larger bulla. There is edema in the cutis, especially joining the large bulla, and below the cellular vesicles. In the upper cutis there is inflammatory infiltration consisting of round cells, wandering connective tissue cells, and some leukocytes especially around the vessels. Apart from that, much pigment can be seen in the upper cutis. (Biopsy report by Dr. Max Jessner, New York Skin and Cancer Unit.)

Course in the Hospital.—The patient remained afebrile throughout her entire stay. She appeared well generally except for the dermatosis. Various measures of local and systemic therapy were employed. The pruritus continued practically uninfluenced except for occasional slight benefit from the antihistaminic drugs. Under each new regime, some improvement would manifest itself in the appearance of the skin and in the stability of the patient. Exacerbations were definitely observed following emotional disturbances and excitation; there were enough of these to make it difficult to evaluate the effect of the treatment utilized. A partial list of drugs administered and procedures follows: autohemotherapy, intravenous calcium gluconate, sulfapyri-

dine, Pyribenzamine Hydrochloride, Benadryl, Hydryllin, salicylates, low protein diet, thyroid, local applications and medicated baths, sedatives, and laxatives. It should be pointed out that slight progressive improvement seemed to follow the administration of thyroid extract, although its effect may have been coincidental to the natural evolution of the disease.

This patient was subject to frequent spells of morbid depression and crying. Occasional excitation bordering on hysteria was observed. Psychiatric aid was contemplated. Reassurance was our main forte. As a further psychotherapeutic measure and, at the same time to permit her to escape from an over-anxious and highly neurotic family, an out-of-town consultation was proposed.

The improvement was not dramatic. There was a slow regression of the lesions. Hyperpigmentation and pruritus were still present, one month following discharge from the hospital. The menses had been restored. The sedimentation rate had returned to normal. The basal metabolic rate had risen to minus 6 per cent.

The diagnosis of herpes gestationis is favored by the following: time of onset, course and character of the eruption, laboratory findings of blood and blister eosinophilia, and biopsy specimen showing the histologic changes of lesions characteristic of herpes gestationis.

DISCUSSION

This case report of herpes gestationis reveals an intriguing problem in the differential diagnosis and management of an allergic, pregnant young woman with a refractory bullous dermatosis. It uniquely demonstrates the need for a co-operative and collaborative medical approach in its successful management. It also provides a source for speculation and theorization concerning the possible mechanisms of its etiology and pathogenesis.

It may be categorically stated that it is a comfort in medicine to establish a diagnosis based on specific bacterial or metabolic causes for which there exist specific antibiotics, chemical, and glandular therapy.

In consideration of this case of herpes gestationis, several possible mechanisms, such as allergenic, endocrine, virus, toxic, and psychosomatic, were felt to be functioning independently or collectively. These shall now be considered in order.

A reaction pattern common to the establishment of a diagnosis of allergy was present. This young woman had a known history of urticaria and perennial allergic rhinitis, and a strong familial history of allergy. She developed a highly pruritic, bullous dermatosis. Eosinophiles were prominent in the peripheral blood and in the vesicular fluid. The antihistaminic drugs provided some relief. These observations may be considered as suggestive of a possible allergic mechanism. This theory may imply the induction of a state of autosensitization to some exciting factor in pregnancy. A progressive state of hyposensitization may have been achieved spontaneously in this patient.

This case also followed a pattern ascribed to a relatively uncommon polymorphous eruption known as dermatitis herpetiformis. Sulzberger has described herpes gestationis as a "morphologically characteristic eruption of dermatitis herpetiformis occurring during pregnancy and terminating

with, or soon after delivery." He claims that this suggests a possible endocrinologic basis for this dermatosis or a sensitization reaction to the exciting factor in pregnancy.

A complicating endocrine factor in the form of hypothyroidism was suggested by the clinical evidence of weight gain and repeated low basal metabolic rates. Improvement in the dermatosis followed the administration of the thyroid extract. This introduced the possibility of the thyroid functioning in the general restoration of endocrine balance. In pursuit of the establishment of a diagnosis of endocrine allergy, hormonal testing, according to the technique of Zondek and Bromberg,[4] was commenced but not completed.

The possible role of virus infection could not be readily dismissed. Was the skin response a manifestation of an id reaction to some allergen, possibly virus, through hematogenous spread? This theory has been propounded by Urbach,[3] who had observed erythema multiforme frequently following herpes labialis in seven to ten days. Erythema multiforme was a tentative diagnosis in the case under discussion.

In support of the toxic theory, herpes gestationis is believed by some to be due to the absorption of ferments from disintegrating chorionic villi exerting a secondary toxic effect on the vasomotor nerves.

It became important to establish the benign character of the skin reaction. The pemphigoid appearance coupled with the severe depression of the patient was misleading.

It was also necessary to establish the prognosis as to ultimate complete recovery. The tendency to recurrence, increased capacity for sensitization reactions at the involved sites, and the potential effect of subsequent pregnancies were among the problems to be considered.

The over-all picture was frequently confused and blurred because of the presence of a marked anxiety neurosis with depressive features and evidences of neurotic and self-induced excoriations.

This case has been reviewed with the hope that it will provoke discussion and suggestions, also to re-emphasize the need for and importance of collaboration with our colleagues in the allied fields in the management of a difficult case.

SUMMARY

1. A case report of herpes gestationis is added to the relatively scarce literature on this particular dermatosis.
2. The differential diagnosis is briefly reviewed.
3. The problems in management are presented.
4. Possible mechanisms of etiology are considered.

(References on Page 183)

SNAKE VENOM (ANCISTRODON PISCIVORUS) IN THE TREATMENT OF CHRONIC URTICARIA

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MOCCASIN venom was introduced by Peck for the treatment of various conditions characterized by a tendency to hemorrhage.[7] Peck and Sobotka[9] showed that previous injections of moccasin venom rendered a large number of the injected rabbits resistant to the Shwartzman phenomenon. Peck noted further that only certain venoms were capable of producing this refractory state. Moccasin venom was particularly effective in this respect, but even individual venoms from the mocassin snake varied in their content of the factor or factors which were responsible for the production of the refractory condition. Subcutaneous injections of moccasin venom were employed as a therapeutic measure in chronic hemorrhagic purpura. It was reported by Peck[8] to be of value in twenty-two of thirty-four cases on which it was used. It was reported to be of value in seventeen out of twenty cases of functional uterine bleeding.[4] Forty-two patients with recurrent epistaxis without any form of blood dyscrasia were treated with subcutaneous injections of moccasin snake venom. The venom therapy was effective in practically all instances either in completely arresting and controlling the nasal bleeding or in markedly diminishing it in amount and frequency.[5]

In our first case, snake venom was used in a case of urticaria which failed to respond to the conventional treatment. This patient frequently developed spontaneous ecchymoses and bruised easily, and for this reason it was hoped that the snake venom might alter the capillary permeability sufficiently to prevent the development of urticaria. The next two cases were very similar except that the tendency to bleed was not as pronounced in the third case. Three subsequent cases with no tendency whatsoever to bleeding are reported to indicate that the beneficial results are not due solely to the abnormality in the bleeding mechanism.

CASE REPORTS

*Case 1.**—Mrs. H. W. M. was a widow, aged fifty-eight. Her chief complaint was of urticaria since March 1, 1948. Her first visit to me was on August 10, 1948.

Present Illness.—This patient had never had urticaria previous to March 1, 1948; that evening she suddenly began to itch severely, and large wheals appeared over her entire body. This condition persisted; the wheals appeared each night and faded during the day. She was seen by several physicians who prescribed sedatives, colloid baths, citrocarbonates, Pyribenzamine, Benadryl and hydrochloric acid U.S.P. These medications failed to give satisfactory relief.

Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

*The author wishes to express his appreciation to Dr. Hans Krakauer of Boston, N. Y., for permission to report Cases 1 and 6, both of whom were his patients, and also for his help in the treatment of Case 1 and the complete report in Case 6.

Past History.—She had had rheumatic fever, measles, and scarlet fever, all in childhood. She had had a streptococcus sore throat in 1939. An oöphorectomy was performed in 1928, her appendix was removed, and perineal repair was done at the same time. She also suffered fractures of various bones at different times. Her menopause had occurred in 1937. She had had no bleeding or discharge since that time. On various occasions ecchymoses were noted on her skin and she "bruised easily" for as long as she could remember. There was no family history of allergy.

Physical Examination.—The positive findings consisted of generalized urticarial wheals over her chest, back, abdomen and extremities. The wheals varied in size from 3 to 10 mm. The nasal mucous membrane was covered with crusts: what mucous membrane could be seen appeared to be normal. Her teeth were in good repair. Tonsils were small and not infected. No lymph nodes could be palpated in her neck. Her chest was normal, as was her heart. On examination of her abdomen there was slight tenderness elicited on palpation. A scar in the right lower quadrant was well healed; no organs were palpable. Arthritic changes were noted in her fingers, knees and ankles. Reflexes were present and equal. Blood pressure was 158/80. Pulse was 64 per minute.

Laboratory Studies.—Urine was negative for albumin and sugar. Hemoglobin was 84 per cent. Sedimentation rate was 17 mm per hour. Wassermann test was negative. Interdermal skin tests with eighteen common inhalant substances were negative.

Subsequent Course.—A search for focal infection was made. Her teeth were negative for alveolar abscesses by x-ray. A course of sulfadiazine failed to improve her condition. No improvement was obtained by use of calcium gluconate intravenously. The vegetable protein diet of Cooke[1] was tried without improvement and then the animal protein diet,[1] also without improvement. Treatment with histamine phosphate (1:1000) 0.1 cc to 0.3 cc was tried. A slight improvement was noted. She became very flushed and had a severe histamine response at 0.3 cc of (1:1000) so that this dose was repeated daily for one month. She still failed to gain tolerance and was changed to Histamin-Azo-Protein. A test for moccasin venom was made November 2, 1948, with 1/10 cc of 1:3000 (Lederle); a hemorrhagic area 1.5 cm was noted after one hour. Her subsequent course was as shown on chart on opposite page.

Case 2.†—Miss L. K. D., aged forty, was a white spinster whose chief complaint was of urticaria present since 1938. Her first visit to my office was on September 27, 1948.

Present Illness.—From 1938 until 1943 this patient had giant urticaria which persisted until 1943, when it disappeared spontaneously. She was entirely free from this condition from 1943 until 1947, when the urticaria recurred and persisted. She had been treated with injections of epinephrine, ephedrine sulfate, phenobarbital, Pyribenzamine (which was discontinued because it made her feel "peculiar"), discontinuation of all medication for one week, aminophyllin suppositories every six hours, Hydryllin, intravenous procaine, and calcium gluconate, all without improvement.

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†The author wishes to express his appreciation to Dr. Harold Robins for referring this patient and for the use of his case study in this publication.

CASE 1

Date	*Hist.-Azo-Protein*	*Moccasin Venom (1:3000)*	*Notes*
11/12/48	0.1 subcut.	0.1 subcut.	
11/20/48	0.1 subcut.	0.1 subcut.	Repeated due to several wheal and ecchymoses at site of snake venom.
11/28/48	0.4 subcut.	0.1 subcut.	Hives are better.
12/ 4/48	0.4 subcut.	Discontinued because of sore arm.	Urticaria improved.
1/21/49	0.5 subcut.		
2/ 5/49	0.7 subcut.		
2/11/49	0.8 subcut.		Had severe urticaria again.
2/18/49	0.6 subcut.	0.05 subcut.	
2/26/49	0.5 subcut.	0.1 subcut.	Urticaria improved.
3/12/49	0.6 subcut.	0.1 subcut.	No urticaria.
3/21/49	0.6 subcut.	0.1 subcut.	No urticaria.
3/26/49	0.7 subcut.	0.1 subcut.	No urticaria.
4/ 2/49	0.7 subcut.	0.1 subcut.	No urticaria.

Past History.—She had had a non-thrombocytopenic purpura on a vascular basis since May, 1948, generalized fibrositis and causalgia of the left arm, "growing pains" in childhood, osteomyelitis of the mandibular and maxillary bones in 1935, "hands became stiff and sore" 1932, right knee became stiff and swollen 1935, cystitis 1942, and menorrhagia every two to three weeks in 1927 which improved after therapeutic x-ray. It recurred November, 1943, and was corrected only after a complete hysterectomy. The following fractures were sustained by this patient: left shoulder, January 18, 1944; fracture of left wrist, February 20, 1947. An appendectomy was performed in 1927 and a tonsillectomy in 1924. All her teeth had been extracted between 1930 and 1935. Other allergic conditions consisted only of migraine headaches 1930 to 1935, which disappeared when milk was excluded from her diet. There was no family history of allergy.

Physical Examination.—The patient was a well-developed, poorly nourished white woman. Her skin showed various sized urticarial wheals distributed generally over her entire body. Her eyes were not remarkable. Her nose showed the mucous membrane to be pale pink, no discharge was seen, the nasal airway was adequate, and the septum was deviated to the left. Upper and lower dentures replaced the extracted teeth. The tonsils were removed completely. The posterior pharynx was normal. No nodes were palpable in the neck, and the thyroid was not palpable. Breathing was vesicular, and no râles were heard. Her heart was not enlarged, and the tone was good. No murmurs could be heard. The rate was 76 per minute. The rhythm was regular. The blood pressure was 90/70. The pulse was 76 per minute. The abdomen showed scars over the midline of the lower abdomen and at right rectus. There was slight tenderness over the ascending and transverse colon on palpation. Her extremities showed the dorsalis pedis and posterior tibial arteries to be palpable bilaterally. Her left fifth finger did not

flex, and the left fourth finger could not be extended completely. Her left wrist was slightly limited in extension, flexion, and rotation. Her left elbow was tender on palpation, but the motion was good. Good motion was obtained in both shoulders, but her left shoulder was painful when put above a right angle. Her hips showed good motion but were painful, especially on adduction. The knees were normal. Her left ankle was swollen. Her feet were not remarkable. The vertebrae were normal. Rectal examination showed the sphincter tone good. No hemorrhoids were seen. Neurological examination showed that all tendon reflexes were somewhat hyperactive.

Laboratory Studies.—Blood work: red cells 4,800,000, with 13.4 gm hemoglobin; white cells 5,500; differential, 21 bands, 46 filamented, 1 eosinophil, 1 basophil, 30 lymphocyte, 1 monocyte. Sedimentation rate was 11 mm per hour. Glucose: 110 mg per cent, urea n. 12 mg per cent, calcium 10.1 mg per cent, phosphorus 3.0 mg per cent, albumin 6.2 mg per cent, globulin 2.3 mg per cent, uric acid 3.2, Hematocrit: 49 mm. Bleeding time was 4 minutes. Clotting time was 3½ minutes; retractibility was normal. Platelets were 380,000, prothrombin time 13 seconds. Rumpel-Leede (tourniquet test) was positive.

Urine: Normal except for an occasional white cell.

Bone marrow: Diagnosis of mild non-thrombocytopenic purpura.

Intradermal skin tests:

Positive reactions:	plaintain	feathers	silk	rye	almond
	house dust	tobacco	sandfly	tea	brazil nut
	cat hair	insecticides	milk	pork	pistachio
	dog hair	flaxseed	rice	crab	

Subsequent Course.—Treatment with Neo-Antergan, animal protein diet,[1] injections of histamine phosphate, desensitization with dust and feathers, and avoidance of positively reacting foods and inhalants resulted in a moderate improvement in the patient's urticaria for twenty-one days and then a severe recurrence Moccasin venom and histamine phosphate were administered as shown on chart on opposite page.

Subsequent Course.—The urticaria ceased to be a problem, and although she remained under treatment for her other ailments her physician reported that she has had no further attacks of urticaria.

Case 3.—Mrs. E. D. was a white housewife, aged thirty. Her complaint was of urticaria present since June, 1948. Her first visit to my office was on January 6, 1949.

Present Illness.—This patient had urticaria in June, 1948, which recurred daily. She was given trial diets, vitamins, and Pyribenzamine, all by her family physician; but satisfactory improvement was not obtained.

Past History.—She had had infantile eczema which persisted until the age of twenty-nine. In childhood she suffered from asthma and allergic rhinitis, which recurred mildly in 1944 and persisted. She also had measles and pertussis in childhood and a tonsillectomy in 1924. She "bruised easily" as long as she could remember. Her son had "food allergy."

Physical Examination.—She was a well-nourished, well-developed white woman. Her skin showed scattered urticarial wheals around 4 mm in diameter distributed particularly behind her ears and along the vertebral area. Eyes were normal. The nasal mucous membrane was pink-white in color and slightly edematous. There

CASE 2

Date	*Histamine Phos.(1:1000)*	*Moccasin Venom*	*Notes*
10/26/48	1/20 cc	0.1 cc(1:3000) intradermal	A wheal 2 by 2 cm with a purpuric area appeared in 1 hour. Purpuric area persisted for 7 days at site of intradermal venom.
11/ 2/48	1/20 cc	0.1 cc(1:3000)	Improved since 10/29/48.
11/16/48	1/20 cc	0.1 cc(1:3000) subcutaneously	Clear until 11/2, then recurred.
12/14/48	1/20 cc	1/20 cc(1:3000)	Severe reaction after last injection. Urticaria improved 7 days after last injection. No urticaria at present.
1/ 4/49	1/20 cc	1/20 cc(1:3000)	No hives.
1/18/49	1/20 cc	0.1 cc(1:3000)	Recurrence of urticaria 1/11/49. Present on and off since.
2/ 1/49	1/20 cc	0.1 cc(1:3000)	No hives.
3/10/49	None	1/20 cc(1:3000)	Two mild attacks of urticaria in the interval following a nerve block.
4/14/49	1/20 cc	3/10 cc(1:30,000)	Had a sore arm from last snake venom injection. Had a mild recurrence of urticaria.
4/19/49	1/10 cc	6/10 cc(1:30,000)	No hives.
4/28/49	2/10 cc	7/10 cc(1:30,000)	No hives.
5/ 5/49	None	7/10 cc(1:30,000)	Occasional hives.
5/12/49	None	7/10 cc(1:30,000)	No hives.

was no obstruction to the airway. The teeth were good and no apical abscesses were disclosed by x-ray. The tongue was normal. The tonsils were out completely. The posterior pharynx was clear. The neck showed no nodes to be palpable, and the thyroid was not palpable. The lungs were clear. Her vital capacity was 2.9 liters. Her heart was normal. Her blood pressure was 110/78. Her pulse was 76 per minute. No scars or abnormalities were found on the abdomen on palpation. There was some tenderness over both kidney areas on percussion. Extremities were not remarkable. Reflexes were physiological.

Laboratory Studies.—Hemoglobin was 92 per cent. Sedimentation rate was 5 mm per hour. Urine was negative for albumin and sugar. Microscopically her urine showed amorphous urates with an occasional white and red cell. Intradermal skin tests showed the following positive reactions:

orris root	tobacco	cornmeal	salmon	red pepper
house dust	milk	coffee	walnut	
feathers	oat	chocolate	chestnut	

Course: The patient was instructed how to make her bedroom dust- and feather-free and to avoid reacting substances. No substantial improvement was

noted after seven days. Injections of moccasin venom and histamine were given as follows:

Date	*Histamine Phos.(1:1000)*	*Moccasin Venom*	*Notes*
6/11/49	1/10 cc	1/20 cc(1:3000)	
6/18/49	2/10 cc	1/10 cc(1:3000)	Improved.
6/25/49	3/10 cc	2/10 cc(1:3000)	One attack of urticaria in interval.

The patient subsequently was interviewed at intervals for several months. She remained free of urticaria following the injections of June 25, 1949. At her latest interview November 2, 1949, she stated that she had had no recurrence of urticaria. She observed that she continued to "bruise easily" and that the only time she was free of bruises was during the period she received moccasin venom.

Case 4.—Mr. S. D. was a white male, thirty-three years old, and his chief complaint was of urticaria since 1941 (eight years).

Present Illness.—This man stated that he was perfectly well until 1941, when while in army service in Louisiana, he noticed a "lump in his throat" and urticarial wheals over his body. He was admitted to the station hospital, where he was studied. Various diets were tried. Injections of epinephrine were given. No cause for this condition could be determined, and no improvement resulted from treatment. The urticaria persisted, and he was given a medical discharge on the basis of urticaria severe. This condition persisted up to the time he was seen at this office in spite of study at a Veterans Hospital, continuous care from a private physician and outpatient treatment from the Veterans Administration Clinic.

Past History.—The patient had no atopic family history. His mother had diabetes. The only infection he could recall having was influenza in 1947. He had a tonsillectomy in 1942. Had had gonorrhea.

Physical Examination.—The patient was a well-developed white man. His skin showed dermatographism with small urticarial wheals scattered over his body. His pupils reacted normally. His nasal mucosa was of a red color, and it was edematous. No nasal discharge was present, and there was no nasal occlusion. His teeth were normal on examination. A small tonsillar stub was present in the right tonsillar fossa, but it apparently was not inflamed. The left tonsil was removed completely. No cervical lymph nodes were palpable, and the thyroid gland was not palpable. Breathing was vesicular upon auscultation. His heart was normal as were his abdomen, extremities, rectum, and prostate.

Laboratory Studies.—Sedimentation rate was 6 mm per hour. Hemoglobin was 110 per cent. Urine was negative for albumin and sugar. . The Kahn test was negative. Intradermal skin tests showed the following positive reactions: timothy, ragweed, plantain, Alternaria, orris root, house dust, horse hair, horse serum, cat hair, dog hair, feathers, tobacco, insecticides, flaxseed, cottonseed, kapok seed, silk, sandfly, cattle hair, wool, glue, goat hair, rabbit hair, gum ghatti, elm, hops, lobster, nuts, and other foods. The following remedies were tried without success: Decapryn Succinate, 2848 (Winthrop), phenobarbital and vitamins, and injections of histamine phosphate.

During the period of observation it was noted that this patient had a history of early and late hay fever; therefore, treatment for grass, plantain, and ragweed pollen was instituted. No substantial improvement in this patient's urticarial condition was noted.

Date	*Moccasin Venom*	*Remarks*
6/29/49	1/10 cc intraderm. (1:30,000)	Large wheal, no ecchymosis.
7/ 8/49	2/10 cc subcut. (1:30,000)	
7/11/49	4/10 cc subcut. (1:30,000)	Arm was sore.
7/14/49	3/10 cc subcut. (1:30,000)	
7/21/49	4/10 cc subcut. (1:30,000)	
7/28/49	5/10 cc subcut. (1:30,000)	
8/ 4/49	6/10 cc subcut. (1:30,000)	
8/11/49	7/10 cc subcut. (1:30,000)	
8/20/49	8/10 cc subcut. (1:30,000)	Better in regard to urticaria this year than previous years.
8/27/49	8/10 cc subcut. (1:30,000)	
9/ 2/49	9/10 cc subcut. (1:30,000)	Very few hives.
9/10/49	1/10 cc subcut. (1:3000)	
9/13/49	2/10 cc subcut. (1:3000)	
9/17/49	3/10 cc subcut. (1:3000)	
9/23/49	4/10 cc subcut. (1:3000)	
9/28/49	5/10 cc subcut. (1:3000)	
10/ 5/49	6/10 cc subcut. (1:3000)	
10/12/49	7/10 cc subcut. (1:3000)	
10/14/49	8/10 cc subcut. (1:3000)	Rarely has hives.
10/21/49	9/10 cc subcut (1:3000)	
10/28/49	1 cc subcut. (1:3000)	Hives no longer seen.
11/ 4/49	1 cc subcut. (1:3000)	
11/11/49	1 cc	
11/26/49	1 cc subcut. (1:3000)	
12/ 3/49	1 cc subcut. (1:3000)	
12/ 9/49	1 cc subcut. (1:3000)	
12/16/49	1 cc subcut. (1:3000)	Rare urticarial wheal only.

Case 5.—Mr. N. C. was a white man, aged twenty, whose chief complaint was of urticaria since August, 1946.

Present Illness.—His illness started with a generalized urticaria while he was with the U. S. Military Police and on furlough in Holland during August, 1946. He was admitted to the station hospital for this condition September to October, 1946. In spite of treatment the urticaria remained until June, 1947, when it disappeared quite suddenly following treatment with Torantil. He was free from urticaria until February 28, 1948, when the urticaria again recurred and persisted until he was first seen at my office March, 1948.

Past History.—This patient showed "excessive reactions" to bee stings from early childhood; besides this there was no past history of allergy. Past infections consisted of measles, mumps, pertussis. He had a tonsillectomy in 1940. There was a family history of allergy inasmuch as a sister had hay fever, and his mother and an uncle both had urticarial attacks.

Physical Examination.—His blood pressure was 120/60. His pulse was 104 per minute. An occasional urticarial wheal of small size was seen on his neck. The examination was otherwise negative.

Laboratory Studies.—His hemoglobin was 100 per cent. Sedimentation rate was 9 mm per hour. Blood showed the differential to be 63 filamented, 7 bands, 29 lymphocytes and 1 eosinophil. His stool was negative for ova. Urine was negative for albumin and sugar. By intradermal skin tests, he showed positive reactions to ragweed and plantain pollen, house dust, and feathers. No causal relationship could be elicited by history between the positive skin reactions and clinical symptoms.

Treatment.—Dexidrine tablets, trial diets, avoidance of feathers, injections of histamine phosphate, injections (intravenous) of calcium gluconate, Pyribenzamine tablets, Thephorin, injections of epinephrine subcutaneously, phenobarbital, sulfasuxadine, autohemotherapy, Torantil, and tonic were all given either separately or simultaneously. No definite improvement resulted.

Course.—He continued to have symptoms until May 29, 1948, when the urticaria disappeared spontaneously and did not recur until May, 1949 (one year interval). His second bout was treated as follows:

Date	*Drug*	*Dose*	*Condition*
5/18/49	Histamine (1:1000)	1/10 cc	Mod. number urticarial wheals.
5/21/49	Histamine (1:1000)	2/10 cc	Mod. number urticarial wheals.
5/23/49	Histamine (1:1000)	3/10 cc	Slight improvement.
5/26/49	Histamine (1:1000)	4/10 cc	Many urticarial wheals.
5/29/49	Histamine (1:1000)	5/10 cc	Slightly better.
6/ 1/49	Histamine (1:1000)	6/10 cc	Very many urticarial wheals.
6/ 4/49	Histamine (1:1000)	7/10 cc	Very many urticarial wheals.
6/ 8/49	Combisul gram 0.1 PCTID		Very many urticarial wheals.
6/11/49	Combisul gram 0.1 PCTID		Very many urticarial wheals of smaller size.
6/15/49	Combisul gram 0.1 PCTID		Very bad.
6/21/49	Moccasin venom (1:30,000)	1/10 cc	Very bad.
6/25/49	Moccasin venom (1:30,000)	2/10 cc	Urticaria present but definitely improving.
7/ 5/49	Moccasin venom (1:30,000)	2/10 cc	Only one attack of urticaria in interval.
7/13/49	Moccasin venom (1:30,000)	4/10 cc	Improving.
7/23/49	Moccasin venom (1:30,000)	5/10 cc	One mild attack only.
8/ 6/49	Moccasin venom (1:30,000)	1/10 cc	Huge local reaction at site of injection lasted 3 days. Urticaria better.
8/13/49	Moccasin venom (1:30,000)	1/10 cc	
8/20/49	Moccasin venom (1:30,000)	2/10 cc	
8/27/49	Moccasin venom (1:300,000)	3/10 cc	Arm extremely swollen after last injection, urticarial wheals appeared on it. Swelling lasted 3 days.
9/12/49	Moccasin venom (1:300,000)	5/10 cc	
9/19/49	Moccasin venom (1:300,000)	6/10 cc	No reaction, no urticaria since 9/12/49.
9/26/49	Moccasin venom (1:300,000)	7/10 cc	No urticaria.
10/ 8/49	Moccasin venom (1:300,000)	8/10 cc	No urticaria.
10/12/49	Moccasin venom (1:300,000)	9/10 cc	No urticaria.
10/19/49	Moccasin venom (1:30,000)	1/10 cc	No urticaria.
10/26/49	Moccasin venom (1:30,000)	2/10 cc	No urticaria.
11/ 2/49	Moccasin venom (1:30,000)	4/10 cc	No urticaria.
11/ 9/49	Moccasin venom (1:30,000)	5/10 cc	No urticaria.
11/23/49	Moccasin venom (1:30,000)	6/10 cc	No urticaria.
12/ 2/49	Moccasin venom (1:30,000)	7/10 cc	No urticaria.
12/ 9/49	Moccasin venom (1:30,000)	8/10 cc	No urticaria.
12/16/49	Moccasin venom (1:30,000)	9/10 cc	No urticaria.
12/23/49	Moccasin venom (1:3,000)	1/10 cc	No urticaria.

Patient has felt perfectly well since.

Case 6.—Mrs. J. N. was a thirty-seven-year-old white woman.

Present Illness.—This patient has had recurrent urticaria since 1945. She could find no relationship in her urticarial attacks to food. However, she experienced severe itching following ingestion of aspirin or any other coal tar product.

Past History.—Positive reactions were elicited to the following extracts when tested intradermally: Aspergillus, clove, timothy, hormodendrum, caraway seed, cinnamon, chicken feathers, cocoa, eggs, chicken meat.

Course.—Injections of feathers were given but were discontinued because contact with this allergen had been concluded. Between October, 1947, to October, 1949, this patient had severe attacks of urticaria which did not respond either to intravenous calcium gluconate or to any of the antihistaminic drugs. Snake venom was instituted as follows:

Date	*Hist.-Azo-Protein*	*Moccasin Venom (1:3,000)*	*Remarks*
10/10/49	1/10 cc	1/10 cc	
10/17/49	2/10 cc	1/10 cc	Severe local swelling after injection. No urticaria.
10/24/49	3/10 cc	1/10 cc	No urticaria. Local swelling.
10/31/49	4/10 cc	1/10 cc	No urticaria. Local swelling.
11/ 7/49	5/10 cc	1/10 cc	No urticaria. Local swelling.
11/ 8/49	6/10 cc	Discontinued	No urticaria.
11/15/49	None	1/10 cc	Had urticaria since 11/9/49.
11/21/49	None	1/10 cc	Urticaria much improved.
12/ 2/49	None	1/10 cc	No urticaria.

DISCUSSION

Moccasin venom given empirically appeared to produce definite improvement in six cases of urticaria of unknown etiology. In two unreported cases, no change in the urticarial condition was noted following this treatment. Both of these patients were later found to have definite focal infection, one tonsillar and one of a chronic pyelitis. It is concluded, therefore, that treatment with snake venom will not supplant a careful study in regard to focal infection, food allergy, contact and inhalant allergens, and the usual search for an offending agent. It is only following this study, and in the absence of other causes, that injections of moccasin venom are recommended.

The following properties of snake venom separately or together may account for its beneficial effects in urticarial conditions:

1. Peck and Sobotka[9] showed that it made rabbits resistant to the Shwartzman phenomenon. Moccasin venom was most potent of all venoms in this respect. "The refractory state to the Shwartzman phenomenon produced by venom could conceivably result either from some circulating substance or from a general effect of the venom on the walls of the capillaries, which makes them resistant to hemorrhage. The evidence against a humoral mechanism is the fact that no antibody or other substance which inhibits the Shwartzman reaction has been demonstrated. The refractory condition cannot be transferred passively with serum from refractory rabbits. It has been suggested that the action may be similar to that of a foreign protein, but Peck[6] showed that the factor in moccasin venom which includes the refractory state can be neutralized or inhibited by antivenom in most cases and by normal horse serum in some cases. The inhibitory

effect of venom cannot be due to foreign protein, for the addition of more protein actually prevents the effect of the venom. Antivenom alone in large amounts has no effect on the course of the Shwartzman phenomenon."[11] Evidence indicates that the refractory state in venom-treated animals is due to changes in the walls of the capillaries.

2. Feldberg and Kellaway[3] and Trethewie[12] have shown that histamine and coagulable proteins were liberated by profused tissues when venoms of various snakes were added to the perfusing fluid. There was a strict parallelism between hemolytic activity and capacity to liberate histamine and proteins.

3. Injection of snake venom into intact rabbits[10] produced a decrease of histamine in the blood plasma.

4. A long-sustained liberation of epinephrine was shown by Feldberg[2] after injection of snake venom. This was thought to be due to the formation of lysolecithin in the adrenals. Lysolecithin itself when injected caused a similar output of epinephrine.

Originally it was felt that the effect of the capillaries was the important one in producing improvement in our cases of urticaria, inasmuch as the first three cases had a tendency to ecchymoses after very slight injury. However, when improvement occurred in the latter three patients who failed to have this symptom, it was concluded that the other properties of snake venom were also important in its beneficial effect in this condition.

In the cases numbered 1, 2, 3, and 6 the moccasin venom was used in conjunction with either histamine phosphate or Histamin-Azo-Protein, because the effectiveness of the snake venom in the treatment of urticaria obviously could not be predicated before this study was started. The combined treatment seemed to offer more security to the patient. However, in the first and the sixth cases when the moccasin venom was discontinued the urticaria recurred in spite of the continued use of Histamin-Azo-Protein. In the second case a previous course of histamine phosphate alone had been ineffective in controlling the urticaria. Cases numbered 4 and 5 were treated only with moccasin venom. It was therefore concluded, as the result of these observations, that the moccasin venom was the effective portion of the treatment.

ADMINISTRATION AND REACTIONS

A local reaction to 0.1 cc of a 1:3,000 dilution of standardized moccasin venom, read in one hour, is known as the Peck test to determine capillary fragility. A positive reaction consists of an area of ecchymosis at the site of injection within an hour and denotes increased capillary fragility. It does not occur in the normal individual.

An erythematous swelling at the site of injection occurs from eight to forty-five days following the initial injection as the result of the development of sensitivity to the venom. It is for this reason that an initial

dose of 0.1 cc of a 1:300,000 dilution is recommended and the dose increased by 1/10 cc at intervals of one to seven days, depending on the severity of the condition, going through the various dilutions up to 1:3,000. The final dose of 1 cc of 1:3,000 dilution should be repeated at weekly to monthly intervals until the urticaria no longer recurs.

CONCLUSION

Subcutaneous injection of mocassin venom is an effective treatment in some cases of urticaria.

SUMMARY

1. Six cases are reported of recurrent urticaria which were successfully treated with subcutaneous injections of moccasin venom after other methods of treatment had failed.

2. Such properties of snake venom are discussed which may theoretically account for its beneficial action in this condition.

3. Methods of administration and reactions are discussed.

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HERPES GESTATIONIS

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THE POSSIBLE SIGNIFICANCE OF SCOLIOSIS OF THE SPINE IN THE CAUSATION OF ASTHMA AND ALLIED ALLERGIC CONDITIONS

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THE life of the asthmatic patient is usually not a very happy one. Apart from the gross discomfort which he suffers during an attack, he is often compelled to live in an area in which he can be reasonably comfortable, and this without respect to his occupation or inclination. I feel that any suggestion which tends to improve or cure this complaint should be investigated, and for this reason it may be of interest to give my observations in dealing with a number of these cases over the last five years.

One outstanding sign of asthma in a very large percentage of cases is the asymmetry of the chest wall. This condition conforms to that which is found in scoliosis of the dorsal spine. Other changes are observed, more of a symmetrical pattern in patients whose asthma started in early life, such as the raised shoulders, and are due to enforced expiratory efforts with the aid of the extraordinary muscles of respiration. Further investigation by means of a standing x-ray shows a scoliosis of the spine due in the majority of my cases to a short leg.

A standing x-ray is taken with a movable Potter Bucky stand. The undressed patient faces the tube with his back to the Potter Bucky. A steel wire with a plumb bob at its lower end is suspended between the patient and the stand. This wire rests on the mid-vertical line on the stand. A line is projected forwards on the floor, which is at right angles to the steel wire and to the mid line on the stand. The patient's feet are placed on either side of this line with the heels and toes touching one another. The patient now stands in a normal erect position. It is most important that no attempt should be made to improve the position by making the patient stand like a soldier on parade. The steel wire should not touch the body, but the bob-weight should rest in a position just between and behind the heels. Radiographs are taken of the spine and pelvis with the patient immobile throughout the whole proceedings.

I treat the scoliosis by inserting a solid lift of leather or cork into the shoe on the short side. This lift varies from one-sixth to one-third of an inch according to the degree of the lateral flexion and is fixed inside the shoe where the heel rests. The patient is then treated by manipulation which aims at restoring the spine to its normal position. After a few weeks a vast improvement is noticed in children in the first decade of life. Some parents observe that the asthmatic spasm now more closely simulates an attack of bronchitis and that these attacks grow less in severity until they finally appear like a common cold and then disappear altogether.

With adults approaching middle age, it takes a few months before any marked degree of comfort is reached, although improvement is reported much earlier.

In this article I make special mention of the short leg as a possible cause of asthma because it has occurred so frequently in my patients, but I feel that any other condition, such as a wedge-shaped vertebra, which produces a scoliosis may give similar results. I have also observed in some asthmatic patients who show no short leg or scoliosis that there is a flattening of the normal curve of the spine in the upper dorsal region. This sometimes amounts to a lordosis with a prominence of the sternum corresponding to the vertebrae involved. A common finding also is a dorsal kyphosis combined with a pigeon-chest deformity.

In a closer study of the spine it will be noted that the lateral flexion and rotation covers the area from which the sympathetic nerves emerge from the cord, namely, from D-1 to L-2. We know that the bronchioles derive their nerve supply from the autonomic nervous system. The vagus produces a constriction of the bronchiole, and the sympathetic causes it to relax. Without definite proof to the contrary it may be possible that asthma is due to underaction of the sympathetic rather than to overaction of the vagus, to which latter cause it is so often attributed. The pre-ganglionic sympathetic fibers take origin in the intermediolateral columns of the cord and pass out in the anterior spinal nerves. Those distributed to the bronchi, synapse in the cervical ganglia. Acetylcholine is liberated at the terminals of the pre-ganglionic fibers in the ganglia cells. This substance stimulates the excitor cell in each ganglion and causes the liberation of adrenaline at the endings of the post-ganglionic fibers in the bronchioles.

If through any reason whatsoever there is a diminution in the production of acetylcholine in the ganglion cell, one would expect a diminution in the amount of adrenaline in the nerve terminals in the bronchioles.

In this article I am suggesting that this is exactly what takes place. The sympathetic system is not powerful enough to cause relaxation of the bronchioles, and this is overcome by the vagus and an attack of asthma follows. We are all familiar with the action of epinephrine in these cases. A suitable parenteral dose promptly terminates the attack.

One would expect in an attack of asthma that an urgent call would be made on the chromaffin granules of the adrenal medulla to supply the adrenaline which the bronchioles need. We know that the function of the adrenal medulla is to serve the emergency needs of the body, but in the asthmatic patient this does not take place.

The question arises as to what causes the suppression of the sympathetic adrenal system. Cannon suggests, in explaining traumatic shock in certain instances, that the sympatho-adrenal system is overstimulated by sensory nerve impulses. Freeman, working in Cannon's laboratory, found

that the continuous injection of epinephrine in physiological dosage (0.001 to 0.006 mg per kg of body weight per minute) over a period of two hours caused a fall in plasma volume from 10 to 29.5 per cent. A reduction in blood pressure to considerably below the normal level occurred upon stopping the injection.[1]

I believe that in asthmatic patients the sympathetic adrenal system is continuously overstimulated and exhausted, with the result that any physical or emotional effort catches the patient unawares and is liable to bring on an attack. The low blood pressure which is found so often in asthmatic patients can be explained on these lines.

The association between a malalignment of the spine and an attack of asthma is a subject for speculation. All degrees of scoliosis are met with in patients who never had asthma, but I would hazard the suggestion that because of the spinal deformity, either through torsion of the soft tissues or by passive hyperemia or by some other means, the pre-ganglionic fibers of the autonomic nervous system are subjected to repeated stimulation, and this is the primary cause of the tiring of the sympathetic adrenal system.

The severity of asthma, to my mind, depends on the extent to which the pre-ganglionic fibers to the adrenal medulla are affected. As we know, these fibers synapse in the medulla itself. They leave the cord at about the level of D-8 and D-9, and at their points of origin from the cord they can be subject to the same interference as the other sympathetic nerves.

In dealing with allied allergic conditions one must consider the role played by histamine. Histamine is normally present in the blood and is believed to be derived from the white cells, especially the eosinophil leukocytes. In their effects upon the capillaries, blood pressure, and bronchioles, histamine and adrenaline are antagonistic, and adrenalectomized animals show increased susceptibility to histamine administration.[2] Histamine is a vasodilator and constrictor of the bronchioles. The appearance of a specific antigenic protein leads to the release of histamine in the blood, and in a subject with an unstable vasomotor system it can happen that the release of this substance in the tissues may be responsible for migraine headaches, hay fever, urticaria, angioneurotic edema, and asthma.

The following paragraph by G. W. Bray[3] is of interest: "O'Keefe (1927) has stated that the manifestations of physical allergy depend entirely on these histamine-like capillary responses, a possibility that Duke admits, and he stresses the significance of Manwaring's view that 'capillary permeability will ultimately be shown to dominate fundamental physiological change in protein sensitization to which all other anaphylactic reactions are secondary.'"

CASE REPORTS

Case 1.—I first saw N. J., a girl, aged eight years, on June 9, 1945. She had weekly attacks of asthma for a year. At her dancing lessons she had difficulty in keeping her balance on tip-toe. On September 19 I took a standing x-ray of her

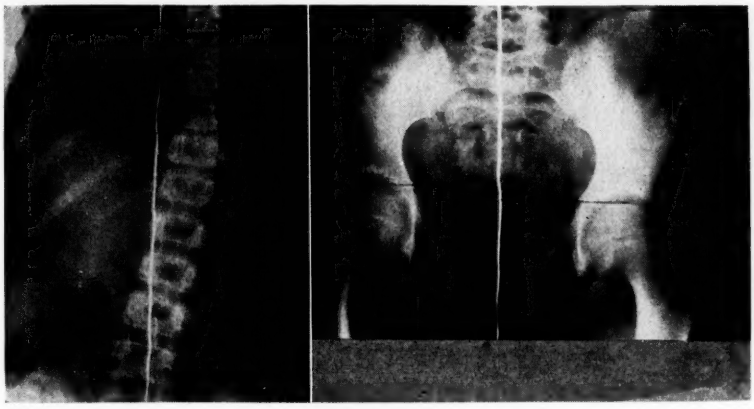

Fig. 1.

spine and pelvis. This x-ray showed a short leg on the left side with a scoliosis convex to the right in the lumbar and to the left in the dorsal region (Fig. 1). A solid leather lift was fixed in the heels of her left shoes.

The asthmatic attacks diminished in number and severity. On December 15 her mother stated that she had occasional slight wheeziness and cough. On July 17, 1946, the mother considered that her child was completely cured.

In a letter dated August 30, 1948, the mother states that N. is now in perfect health and has no signs of asthma whatsover. She is gaining both in weight and in height. She is already 5 feet 3 inches tall, though she will not be twelve until December. She plays tennis and hockey and goes in for swimming and physical culture, and in fact plays and works now like a perfectly normal child. During swimming season (South Rhodesia) she goes to the baths daily and is swimming and diving; yet it is almost an unheard of thing for her to have a cold. When she was first seen, she was hardly ever free from a cold.

In attempting to correct her balance, I accidentally discovered that I apparently cured her asthma. In this first case it will be noticed that the pelvis and spinal films do not superimpose completely. This is due to lateral pelvic sway, which can be eliminated in attention to detail as explained in the text.

Case 2.—I first saw G. L., a boy of nine years and nine months, on January 14, 1946. He had asthma from the age of three, suffering from attacks about once a week.

A standing x-ray taken on January 18 shows a well marked scoliosis of the thoracico-lumbar spine convex to the left with an apparent short leg on the left side (Fig. 2). A solid leather lift one-sixth of an inch thick was inserted into the heels of the left shoes. The boy improved steadily, and on August 19 his mother stated that he had not had an attack of asthma for several months. However, he had another attack on October 8, accompanied by grinding of his teeth. I suggested treatment for worms. Three days later he passed a round worm about 10 inches

long, and the asthma and the teeth grinding disappeared. I believe this attack was induced by the reflex disturbance of the sympathetic nerve supply to the bowel.

In a communication dated February 6, 1948, the mother states that her son is now entirely free from asthma. He plays games at school, swims regularly, and rides a bicycle without any signs of respiratory distress.

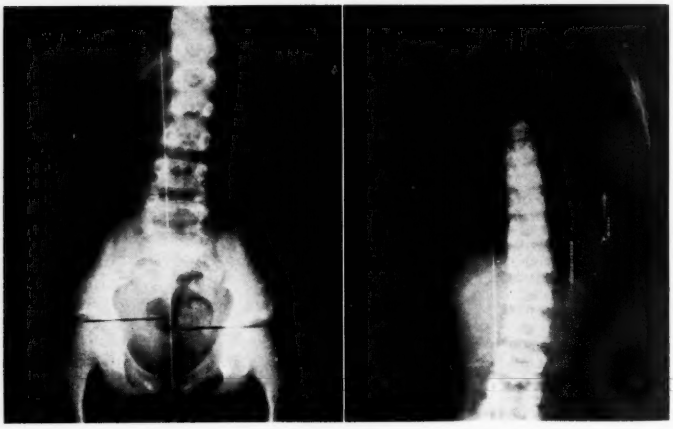

Fig. 2.

Case 3.—I first saw R. H., a boy of eight years, on October 3, 1945. He had suffered from asthma for five years. A standing x-ray taken on October 24 shows a scoliosis convex to the right in the dorsal region and convex to the left in the lumbar region (Fig. 3). Lines dropped at right angles to the mid-vertical wire from the highest points of the iliac crests show a tilting downwards of the pelvis on the right side. A solid leather lift one-eighth of an inch thick was inserted into the heels of his right shoes.

His rate of progress is described by his father as follows (July 20, 1948): "He has had none of his old 'chesty' conditions for several years now. Although he has had whooping cough, chicken pox, and influenza, more recently he has had no recurrence of asthma. He is now able to play games in the ordinary way and is quite a good swimmer, whereas the least physical exertion would have upset him a few years ago."

A standing x-ray of this boy taken on August 7, 1948, with a lift in his right shoe shows the improved condition of his spine (Fig. 3). In fact, it is slightly overcorrected.

SUMMARY

A view is expressed that asthma may be produced by overstimulation of the sympathetic adrenal system. This overstimulation causes a tiring of the system and results in diminished stimulation of the ganglion cells, and thus sufficient acetylcholine is not formed in the cervical ganglia to sufficiently stimulate the post-ganglionic fibers which supply the bronchioles. Owing to this diminished stimulus, sufficient adrenaline is not available to main-

tain the tone of the smooth muscle of the bronchioles. The constricting action of the vagus is almost unopposed, and asthma results.

For the same reason there exists a permeability of the capillary walls of the blood vessels. It is recognizable that a specific antigen protein causes

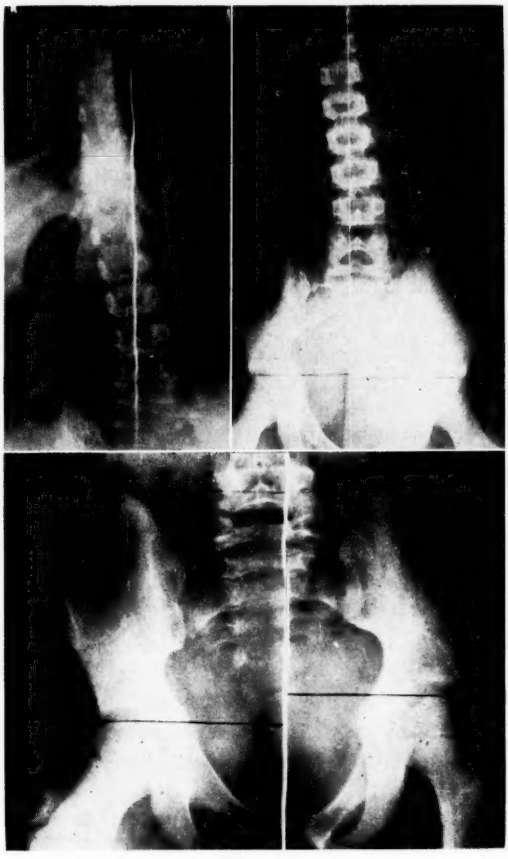

Fig. 3.

the increased release of histamine from the white cells of the blood.* In a person with a balanced vasomotor nerve supply this may cause only a mild feeling of malaise, but when histamine can leak through the walls and is reabsorbed it can be the primary factor in the production of the so-called allergic conditions.

An interference with the alignment of the spinal column in the dorso-

(Continued on Page 219)

SERUM PROTEIN VALUES IN INFANTS FED SOYA-BEAN MILK

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THE present study was undertaken for the purpose of investigating the serum values in infants fed soya-bean milk during the first three months of life.

In the course of caring for infants fed cow's milk formulas the pediatrician may be faced with the necessity of removing milk from an infant's diet because of allergic reactions such as eczema, vomiting, diarrhea, abdominal cramps, and various manifestations in the respiratory tract. Milk sensitivity may be divided into three classifications:[2] (1) species specific factor of cow lactalbumin, (2) common factor to both cow and goat lactalbumin, (3) casein. In group (1) a change to goat's milk is indicated. In group (2) goat's milk may give little improvement. In group (3) goat's milk is valueless. Therefore Hill[1] has stated that he often prefers to do away with milk entirely if milk sensitivity exists. As a substitute for animal milk various "milks" from a vegetable source have been utilized.[8]

The objection has been raised that the proteins derived from vegetable sources are inadequate to support optimum nutrition and may lead to the development of hypoproteinemia. We therefore decided to undertake the following study to determine the effects on serum proteins of infants fed "milk" prepared from soya-beans for the first three months of life.

MATERIALS AND METHOD

The infants studied in this series were all from the newborn nurseries of the Beth-El Hospital and were followed for the period of this study in the Well-Baby Clinic of the same institution. As a preliminary to the study, serum protein values were determined for fifty-five newborns in the nursery in order to have a baseline for comparison. The specimens of blood were drawn on the second and fourth days of life. Two cc of blood was drawn from the femoral vein for each determination. The protein determinations were done by a modified method of Kingsley.[3] Two series of infants were studied. In the first series two infants were placed on soya-bean "milk." Bloods were drawn for protein studies once while in the nursery and once again at three months of age when the study was completed. At the clinic, in addition to a "milk" mixture, these infants received (1) orange juice and a multivitamin preparation at one month

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The vegetable "milk" used in this study was Mull-Soy, which was generously supplied by the Borden Company, Prescription Products Division, New York.

TABLE I. VEGETABLE "MILK" FED INFANTS SHOW PARALLEL GROWTH AND WEIGHT GAINS WHEN COMPARED TO CONTROLS FED COW'S MILK

Case	Sex	Birth Date	Birth Weight	Birth Height	Protein in Nursery*		Follow-Up-Protein			Weight and Height 1st 3 Months		
					1/10/50	1/12/50	2/15/50	3/8/50	4/5/50	2/15/50	3/8/50	4/5/50
J.B. (Mull-Soy)	M	1/8/50	7 lbs. 1 oz.	20½"	T 6.5 A 4.6 G 1.9	6.0 3.8 2.2	T 6.1 A 4.3 G 1.8	6.1 4.6 1.5	6.4 5.1 1.3	Wt. 8-2 Ht. 22"	9-14 23½"	11-12 24"
R.J. (Mull-Soy)	M	1/16/50	7 lbs. 8 oz.	21"	1/17/50 T 6.2 A 3.8 G 2.4	1/20/50 5.1 3.4 1.7	2/ 8/50 T 5.6 A 3.4 G 2.2	3/8/50 5.9 4.5 1.4	4/12/50 6.0 4.1 1.9	2/8/50 Wt. 8-9 Ht. 21"	3/8/50 10-0 22"	4/12/50 11-15 23"
C.T. (Con-trol)	F	1/16/50	6 lbs. 13 oz.	20"	1/18/50 T 6.5 A 3.7 G 2.8	1/20/50 6.5 3.9 2.6	2/8/50 T 5.0 A 3.1 G 1.9	3/1/50 5.2 4.0 1.2	4/12/50 5.0 3.7 1.3	2/8/50 Wt. 8-1 Ht. 20"	3/1/50 9-0 21"	4/12/50 11-9 23"
T.N. (Con-trol)	F	1/13/50	8 lbs. 13 oz.	21½"	1/16/50 T 7.0 A 5.8 G 1.2	1/18/50 6.9 4.3 2.6	2/8/50 T 7.7 A 5.1 G 2.6	3/8/50 7.0 5.7 1.3	4/12/50 7.1 5.7 1.4	2/8/50 Wt. 9-4 Ht. 23"	3/8/50 11-10 25"	4/12/50 13-15 26½"

In this series two patients were on vegetable "milk" and two served as controls.
*Protein Values are in gm per 100 cc.
T—Total Serum Protein. A—Albumin. G—Globulin.

TABLE II. NORMAL GROWTH AND WEIGHT IN INFANTS ON VEGETABLE "MILK" STUDIED FOR THREE MONTHS FOLLOWING BIRTH

Case	Sex	Birth Date	Birth Weight	Birth Height	Protein In Nursery	Protein At 3 Months	Weight and Height 1st 3 Months		
B.S.	M	5/28/50	8 lbs. 9 oz.	21¼"	T 7.3 A 4.7 G 2.6	T 7.0 A 4.6 G 2.4	6/21/50 Wt. 9-3 Ht. 22"	7/19/50 11-4½ 22¾"	8/23/50 13-2 24"
R.R.	F	5/26/50	7 lbs. 7 oz.	21"	T 6.6 A 4.4 G 2.2	T 6.3 A 4.2 G 2.1	6/21/50 Wt. 8-8 Ht. 22"	6/19/50 10-4 23¾"	8/23/50 12-0 25"
H.B.	M	5/19/50	7 lbs. 6 oz.	20"	T 6.5 A 4.4 G 2.1	T 6.1 A 3.8 G 2.3	6/14/50 Wt. 8-12 Ht. 21"	7/31/50 12-15 22½"	8/30/50 15-4 23"
S.M.	M	5/27/50	5 lbs. 13 oz.	20"	T 7.2 A 4.6 G 2.6	T 7.1 A 4.6 G 2.5	6/21/50 Wt. 7-0 Ht. 20"	7/19/50 9-3 21"	8/28/50 12-8 23"
M.T.	F	5/24/50	7 lbs. 6 oz.	21"	T 7.3 A 4.7 G 2.6	T 7.2 A 4.7 G 2.5	6/21/50 Wt. 8-0 Ht. 21¼"	7/19/50 10-2 22¾"	8/23/50 12-1 24"

All the patients in this series were on vegetable "milk."

of age, (2) cereals at two months, and (3) vegetables at three months. Complete physical examinations were done each month and careful appraisal made of growth and development.

RESULTS

The blood serum proteins of the fifty-five infants used for a baseline ranged from 4.2 to 7.3 gm per cent with an average of about 6.3 gm per cent. Figure 1 shows the results in the first series studied. It is readily seen that no hypoproteinemia developed in either the controls or the infants on soya-bean "milk." In the second series, none of the five infants, all of whom were on soya-bean "milk," developed a hypoproteinemia.

Figure 2 shows that the weights of all the patients studied followed a

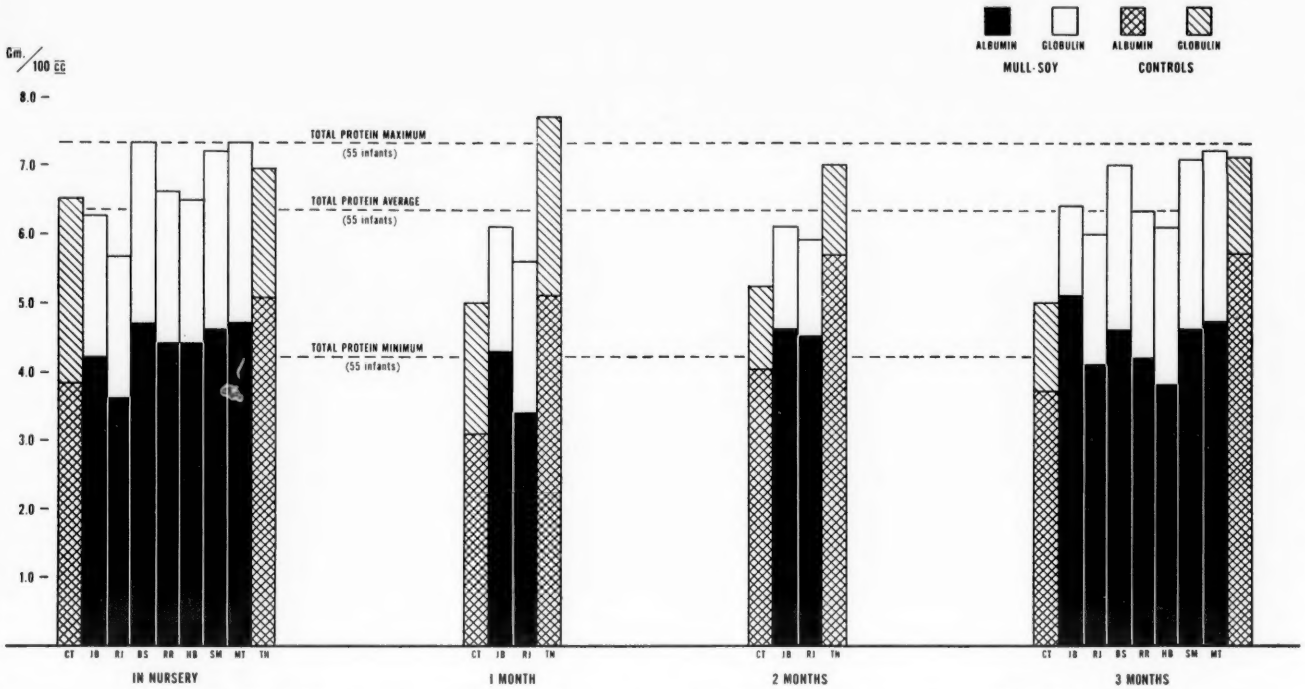

Fig. 1. Similar range of serum proteins in infants fed vegetable "milk" when compared to infants few cow's milk.

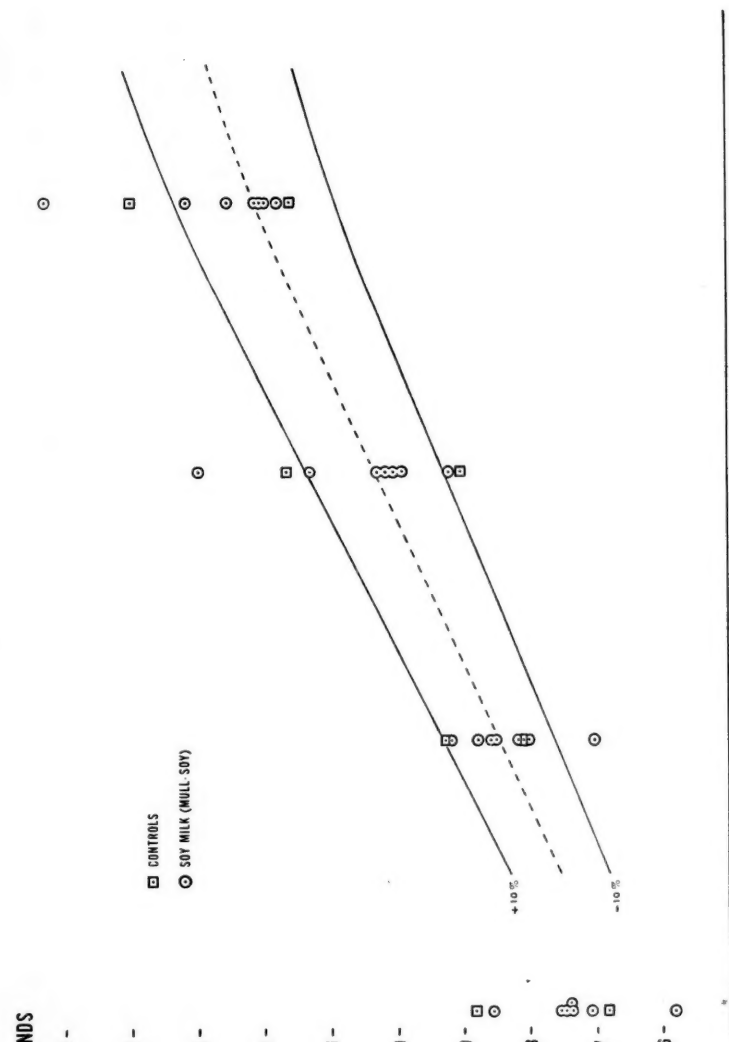

Fig. 2. Normal weight gains of infants fed a vegetable "milk" compared with those fed cow's milk.

normal curve. During the course of the study none of the infants exhibited any clinical manifestations of hypoproteinemia, and in no way could one differentiate clinically between those infants on soya-bean "milk" and the many infants in the clinic fed on other mixtures.

No changes from the normal controls were found in the peripheral blood counts of the infants under study.

DISCUSSION

Our mean value for plasma proteins of normal full-term infants was 6.3 gm per cent, which is in agreement with the findings of McMurray, Roe and Sweet,[4] who, using a modification of the Kingsley method—the same method we employed—to arrive at their results, found a mean value of 6.4 gm per cent.

In a series of eczema cases in which milk substitutes of vegetable origin were used, Wolpe and Silverstone[8] noted that the metabolic needs of the patients were satisfied. They included no blood protein studies in their report. After three years' experience with these substitutes Wolpe[7] concluded that these do not appear to have an advantage for either the milk or a milk substitute diet as the basis of weight gained or lost.

During the course of a nutritional survey, Mirone[5] became interested in a community of men who did not consume meat and whose animal protein intake is low. Since there is a paucity of data upon the blood findings of human beings on prolonged low animal protein intake, she decided to conduct a blood study of these men. The eleven men studied were on a vegetable diet from twelve to forty-seven years. The subjects were never allowed meat, poultry, or fish. The daily animal protein ingested was the milk added to coffee. For 277 out of 365 days a year these men had an intake of 5.7 grams a day of animal protein. The National Research Council's recommended daily protein allowance is 70 grams, of which half or 35 grams should preferably be of animal origin. All the blood studies performed were within normal limits. From these studies Mirone concluded that either the National Research Council's recommended requirement is too high, vegetable protein combinations can be substituted for animal protein, or other chemical determinations might reflect the low intake.

Schick[6] stated that he had never seen any adverse effects from a diet in which the proteins were largely of vegetable origin.

In our study we found no alterations in the serum proteins of infants fed vegetable proteins for the first three months of life. In none of the children did hypoproteinemia develop. Since after the first three months of life other foods are added to an infant's diet from which he can obtain animal proteins, we feel that one can use a soya-bean "milk," where indicated, without fear of detrimental effects being caused by the diminished intake of animal proteins.

(Continued on Page 204)

COW'S MILK ALLERGY IN INFANTS

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ONE baby's formula may be another baby's poison." Although so many babies thrive on cow's milk feedings, others may be distressed by simple colic or become desperately ill as a result of an allergy or sensitivity to cow's milk. Milk is a common factor as a cause of symptoms in infants and children.[11,12] This study is primarily a clinical analysis of 140 infants allergic to cow's milk, whose symptoms were almost immediately relieved by elimination of milk and substitution of soy milk.* Various complicated and expensive diagnostic tests, treatments, and even operations had been performed in an effort to cure these unhappy babies, because milk allergy was not recognized as the cause of the symptoms. Piness[26] in 1925 called attention to allergic manifestations in infants caused by food. Most pediatric textbooks barely mention the consequences of milk allergy. Several clinical reports[20,21,29] mention various groups of symptoms, but most stress only the gastrointestinal upsets. A multiplicity of strange, baffling, serious and apparently unrelated clinical syndromes occur as a result of milk allergy. The type of symptoms depends on the tissue or organ affected as well as the results of the pathological mechanism of allergic disease (edema, spasm of smooth muscle, and mucus secretion) on the particular tissue involved. This explains the reason why so many (fourteen) varied symptom complexes were present in these infants.

Early recognition of milk allergy in infants, then accurate diagnosis and treatment, is more urgent now than in the past due to the present tendency to avoid or discontinue breast milk in favor of cow's milk.[5,6] Many infants who are happy while on breast milk develop various manifestations of milk allergy when put on a cow's milk formula. Apparently cow's milk allergy is not transmitted to the infant through the mother's milk, even though the mother may be allergic to milk (Ratner[28]). Previous studies by the author[10] and others[27] have stressed the importance of early recognition and treatment of the allergic state in infants in order to prevent or minimize major allergy in childhood or later life. The early recognition of milk allergy in infants therefore assumes greater significance.

PLAN OF STUDY

As stated above, this is a *clinical study* of 140 patients in an average office practice. Most of these babies were seen during their first month of life and others from one to nine months of age. They included pre-

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*Mull-Soy furnished by The Borden Company.

mature and full term, males and females, white, colored, and orientals. The diagnosis of milk allergy was accepted when the clinical symptoms were relieved by the complete removal of milk from the infant's diet and the substitution of soybean milk, and when these same symptoms recurred when cow's milk was again added to the diet. All infants received a thorough physical examination to rule out other etiological factors. If the distressing symptoms were not relieved by discontinuing cow's milk and substituting soy milk, it was assumed that some other cause, other than milk allergy, was responsible and further investigation was conducted.

This group does not include babies who were on goat's milk or other milk substitutes; those eight babies (6 per cent) who were unable to tolerate (allergic?) soy milk; those who, although able to take soy milk, were not relieved of their symptoms; or those in whom some physical or other factor than milk allergy was proven to be the cause of symptoms.

The symptoms began in most infants at two to four weeks of age, when milk was still the only food in their diet. When milk allergy was suspected, it was more rational, simpler, and easier to remove cow's milk from the diet for a twenty-four to forty-eight-hour trial period and substitute Mull-Soy than to start an allergic study. A number of babies were tested by scratch and intradermal skin tests, but the results were indefinite, and testing was discontinued in the latter part of the study. This fact was recently confirmed by Matheson.[23] No indirect or passive transfer tests were done, as the diagnosis and successful treatment was usually an accomplished fact long before this type of test would have furnished additional information. These tests might have been an interesting historical medical fact, but this was not the purpose of this clinical research project.

One fact was fairly common in the history of almost all of these unfortunate babies. *The formula had been changed and juggled repeatedly* (in some cases as many as eight times!) in an effort to find the magic factor. Cow's milk (and often goat's milk) modifications had been tried one after another, such as canned, evaporated, condensed, powdered, modified, fresh, and acidified. The carbohydrates suffered similar acrobatics varying from sugar, refined or raw, to Karo or other syrups, dextrin-maltoses, milk sugar, and honey. In addition, the formulas were boiled from five minutes to five hours. Ratner[26] was the first to demonstrate that prolonged heating lowered the antigenicity of milk and other foods. That is why some infants with mild milk sensitivity will continue to do fairly well on a milk formula because the milk has been partially denaturized by boiling.

The magic factor that transformed these unhappy babies into normal infants was an animal-free milk substitute, soy milk. Hill and Ratner[28] have repeatedly stated that goat's milk was of doubtful value in most milk allergy patients because of the crossed reactions of the casein in animal milks. A majority of the infants who are allergic to cow's milk are also

allergic to goat's milk. Many milk substitutes have been advocated and used with some success. These mixtures include taro milk,[13] meat milk,[14,22,31] and various cereal[35] and soybean[16,33] milks, as well as vegetable[35] combinations.

TABLE I. MILK ALLERGY IN INFANTS—140 CASES

	CASES	PER CENT
1. Eczema (rash)	59	42
2. Pylorospasm (spitting up—vomiting)	54	39
3. Colic (severe—excess gas)	40	29
4. "Very unhappy all the time"	27	20
5. Diarrhea	33	24
Mucus in stools	8	6
Blood in stools	6	5
6. Croup and cough	13	9
7. Choking, gagging, and mucus	10	7
8. "Nose cold"—stuffy—runny—pollen hay fever	12	8
9. Constipation—chronic	7	5
10. Asthma (wheezing and cough)	7	5
11. Refuses milk—anorexia	5	4
12. Sneezing (often—spells)	3	2
13. Toxemia (apathetic—listless—cyanosis—collapse)	3	2

Soybean milk has high biologic value and provides for normal growth and development, aided by vitamin supplements, in babies. It is high in unsaturated fatty acids and supplies essential nutritional values of protein, fat, carbohydrates, and minerals. There is no animal protein present. It is reasonable in cost, obtainable at any drug store, and easy to prepare; and most infants take it readily. Sternberg[33] has recently shown that it maintains normal protein levels in the blood. When loose stools result from Mull-Soy feedings, they can be controlled by adding one teaspoonful of Kaopectate to each bottle. If soy milk is absolutely rejected by the infant, goat's milk, Nutramigen, or other substitutes may be tried.

Approximately one of every fifteen infants is allergic to cow's milk to some degree, producing symptoms which would not be present if these babies did not possess this peculiar sensitivity. The tendency to be allergic is bequeathed to these babies by their allergic parents. The degree of intolerance or sensitivity to milk (or other allergens) varies a great deal in each individual; whereas one infant may manifest only mild "colic" or "spitting up" when allergic to milk, another may collapse in shock or even die from a few drops of milk placed upon the tongue.

In this group of 140 unhappy babies who were allergic to cow's milk, fourteen different types of symptoms were present. A detailed description of this bizarre group of symptoms will be discussed. The mother's own descriptions of these allergic complaints will be mentioned to emphasize their peculiarity as well as their similarity to other complaints which might be due to other causes.

Table I itemizes the fourteen major symptom complexes, the total number and relative percentage of each group. In all these cases, the patient would be relieved of his symptoms when soy milk was substituted in the diet, and these same symptoms could be reproduced by again adding a cow's milk formula.

A majority of the infants allergic to milk had several symptom groups at the same time. Two or more major symptoms occurred in eighty-one infants. Eczema accompanied by allergic pylorospasm and colic or both was the most frequent combination. A smaller group, fifty-nine babies, had only one major symptom as a result of milk sensitivity. Their relative frequency is indicated in Table II.

TABLE II. NUMBER OF BABIES HAVING ONLY ONE OUTSTANDING SYMPTOM—59

Eczema (rash)	27
Pylorospasm (vomiting)	11
Diarrhea	9
Colic (severe)	4
Mucus stools—cough—asthma	2 each
Choking and gagging—hives	1 each

1. *Eczema* was the most frequent symptom and was present in fifty-nine cases (42 per cent). The lesions were usually subacute to acute, often itched, and varied from mild to severe. The rash occurred most frequently on the cheeks, forehead, and head (forty-five infants—76 per cent). In eight cases it was present mainly on the body and flexures, and in six infants primarily in the diaper area and on the buttocks. Eczema, of all types, is still the number one problem of infants (Hill).

2. *Pylorospasm* ("vomiters") comprise a large group (fifty-four cases—39 per cent). Although there are many reasons why a baby should and does vomit, these allergic infants were all relieved by avoidance of milk.[6] These "sour babies," who were always spitting up from one feeding to the next, kept their mother busy changing bibs, nightgowns, and shirts until they either outgrew their milk allergy or until a soy bean milk formula was substituted for cow's milk. The baby may have only persistent "spitting up," or he may have serious projectile vomiting. This symptom, like others in this group, is usually present every day, although occasionally, for some unknown reason, they may skip a day. Mucus is frequently found in the vomitus, and this will show a marked eosinophilia when properly stained. Peculiarly, most of these babies gain weight, although they have quite a stormy course. Many have associated colic of varying degrees. They may be constipated or have diarrhea, although usually the bowel movements are fairly normal. Several in this group had had complete gastrointestinal x-ray studies. Balyeat[3] has also described these cases. Four babies had been diagnosed as cases of pyloric stenosis, having classical symptoms of projectile vomiting, constipation, loss of weight, pyloric waves, and marked gastric retention. Operation had been advised. Complete relief occurred in three cases within twenty-four hours after milk was omitted and soy milk added to the diet. One baby had a pyloroplasty without relief, until milk allergy was diagnosed and milk eliminated. Atropine, phenobarbital and antihistamines were of little value in treatment.

3. *"Colic"* was the real bellyache for forty babies (29 per cent). This symptom was usually severe, causing "screaming" and "doubling up" and generalized discomfort which was not relieved by the usual means, such as picking him up, rubbing his back, placing him on the stomach, applying hot water bottles, or giving him more food more often. These babies often cried during and after feedings and would awaken in one half to one hour crying with "violent cramps." They would always seem hungry and were eager to eat at any time. The more often they were fed (demand feeding), the more "bellyache" they had. Many "cried, squirmed and fussed from one feeding to the next."

They were "poor sleepers," passed much gas, and did not seem to be relieved by medicines. Although many had normal bowel movements, others had diarrhea and vomiting with colic. Many so-called "three-months colic babies" deserve a twenty-four-hour trial diet on soy milk to rule out milk allergy as a cause of their complaint.

4. *Diarrhea* was an annoying symptom in thirty-three infants (24 per cent). This consisted of frequent, loose, watery, often curdled, yellow to green stools that irritated and burned their skin and buttocks. Mucus was usually present, and in six cases this was grossly visible in large amounts, which was the reason for bringing the baby to the doctor. Numerous eosinophiles were present in this mucus.[25] A similar number of babies had fairly large amounts of bright red or dark blood, grossly visible in the stool, while many others had small streaks of blood. This has also been described by Rubin.[32] Colic, vomiting, and occasionally dehydration occurred in the severe cases. The trypsin stool test was normal in most cases and doubtful in a few. Several infants had been previously diagnosed as having celiac disease, but the symptoms cleared up immediately on elimination of milk from the diet. Two infants in this group later developed celiac disease. Anderson states that in her series only two of eighty-seven cases of celiac disease had milk allergy. Bloch[4] describes the celiac syndrome due to food allergy.

5. *"Very unhappy all the time"* describes probably one of the most pitiful effects of cow's milk allergy, occurring in twenty-seven infants (20 per cent). This simple description is the most adequate. These babies were "miserable," "cried all the time," "nothing makes him comfortable," "so different from my others," as a result of the colic, pylorospasm, rash, or other symptoms from which he suffered. No old-fashioned or modern remedy would relieve these "wretched" patients, who actually looked the part, until a "miracle occurred," and they became a "changed baby" as soon as milk was removed from their diet. These unfortunate, unhappy infants are probably the counterpart of some older children who suffer from "character changes" and are "problem children" as a result of undiagnosed, untreated, or uncontrolled allergic manifestations. This has

been adequately described recently by Clarke,[8] Alvarez,[1] and Rowe.[30]

6. and 7. *Chest cold.* The most serious, baffling and also most frightening symptoms[24] relate to the respiratory system. "My baby has had a chest cold since birth," "he rattles all the time." "he coughs at any time, often worse at night and sounds croupy," "chokes with mucus, coughs hard, and wheezes, especially after taking the bottle," "noisy, loud, coarse breathing is present almost all the time he is awake." These descriptions adequately describe this group of symptoms. Many in this group had been x-rayed, and four babies had been treated for thymus enlargements. Two babies had been bronchoscoped and one of them two times! Antibiotics of all types and in large amounts had been used in most of these cases. Several had had large series of skin tests. "A miracle has taken place" were the words of a grateful mother whose nine-months-old infant had suffered most of the above symptoms and all the treatments. This "miracle" occurred the day after the baby was given Mull-Soy and all cow's milk and milk products had been removed from his diet. This group comprised twenty-three cases or 16 per cent. A case report is presented to illustrate the complexities of this problem:

An infant eight months old, had had trouble breathing since birth, characterized by a stuffy nose, persistent noisy breathing, choking, and gagging spells due to excessive mucus in his throat. At six weeks of age his physician discovered, by x-ray, a wide, upper mediastinal shadow. The baby received three deep x-ray therapy treatments for an enlarged thymus gland. The symptoms continued and the child was bronchoscoped. This seemed to aggravate the condition for a few weeks. At four months of age bronchoscopy was again performed with apparently negative findings. At five months of age his physicians decided that the infant must be allergic to some food. Orange juice, Pablum, fruit, and vegetables were eliminated one at a time from his diet without success. At seven months of age he was skin tested "to many things," but the results did not furnish much positive information. I saw him when he was eight months old with the same symptoms of mucus in his throat, "rattling breathing," cough and nasal discharge. Physical examination revealed a normal infant except for a thick mucous nasal discharge and a moderate stridor. Smears of the nasal and pharyngeal mucus showed many eosinophiles. This verified the diagnosis of an allergic condition. The mother was asked if the baby had been taken off milk at any time and the answer was "no." Milk was then eliminated from his diet and Mull-Soy substituted. The next day the mother called and said that the child was 100 per cent better and that a "miracle" had taken place. and that he seemed like a normal infant. Milk was the cause of all his symptoms.

8. *Nose colds* that were "present from birth" occurred in twelve infants (8 per cent). "He came home from the hospital with a cold and still has it," "just gets over one cold and has another." "Nose is always running and stuffed up so that he cannot breathe, eat or sleep well." The nasal discharge is often watery or thick, gray, shiny, and stringy and contains many eosinophiles when stained. The discharge persists in spite of drops, inhalations, and "shots." Some infants may cough as a result of a postnasal discharge. Grass pollen hay fever was also present in four of these infants who were only a few months old.

9. *Constipation* which did not respond to all the usual manipulations was present in seven infants. The stools were usually large and hard, causing pain and tenesmus when finally passed with the aid of laxatives, enemas, or suppositories. Normal stools quickly followed removal of milk from the diet.

10. *Asthma,* characterized by wheezing and loud breathing due to expiratory rhonchi was the first symptom in seven patients who were allergic to milk.[24] Coughing and much mucus in the throat were also present. A smear of this mucus showed many eosinophiles, pathognomonic of allergic disease.

11. *Anorexia,* characterized by babies who "fought their bottle," "refused milk," or who kept "spitting out the nipple," was not infrequent. These five infants ate readily when given soy milk and repeated their prior performance when a cow's milk formula was substituted.

12. *Sneezing* occurring in paroxysms of three to ten times, at any time of the day, although more frequently in the early morning, was found in babies who were also allergic to inhalants. This is often associated with a nose cold, but occurred as the only symptom in three babies allergic to milk.

13. *Urticaria* and angioedema occurred in three infants and quickly disappeared with omission of milk.

14. *Allergic toxemia,* the most serious symptom, occurred in only three individuals in this group of 140 sensitive to milk. These infants became listless and apathetic, are "limp as a wet dishcloth," may "sleep a great deal" and "seem depressed," and are actually "poisoned by milk." One baby developed a greyish pallor and became cyanotic, had a convulsion and almost died on two different occasions when given milk. These critically ill infants who suffered from allergic "toxemia" or "collapse" became normal, happy babies as soon as milk was taken away from them. A case has recently been reported[19] where death occurred from milk allergy in a highly susceptible infant.

COMMENT

General physicians (who care for 80 per cent of infants and children), as well as pediatricians, are becoming increasingly aware of the fact that an appreciable number of these patients are allergic to cow's milk.[26] Hill[16] has stressed the point that cow's milk allergy should be expected and encountered more often in infants because the first sensitivity an individual develops is usually to the food or foods most commonly eaten. Since milk is often the only food for the first few months, it is natural to expect some susceptible (allergic) infants to show abnormal manifestations to

this food. The various groups of symptoms are characterized by their *chronicity* and/or *periodicity*, which is the usual pattern in most allergic disease. Complete removal of cow's milk in all forms from the diet of the infant or older child is the one and only effective treatment necessary to relieve their various symptoms.[14] It is amazing to observe how rapidly the symptoms and the illness disappear when soy milk is substituted. Since most babies allergic to cow's milk are also often sensitive to goat's milk, all animal milk should be scrupulously avoided. Ratner states that this is because of the crossed reaction to casein (protein) in animal milks.[28] Glaser[15] makes a good point when he suggests that in families where previous siblings have been allergic to milk, the latest offspring be started on a soy milk formula instead of taking the chance of sensitizing the newborn infant to cow's milk. Many of the babies in this series "outgrew" their allergy to milk within three to four months. This is also true in adults.[27] They were then able to tolerate cow's milk in one form or another, often without difficulty. It has been stated[28] that if an individual drinks excessive quantities of milk, it might "stir up" a latent allergy to milk. This has not been our experience. We have also found no correlation between milk allergy in the infant and the amount of milk ingested by the mother prior to the birth of her baby. He usually inherits the tendency to become allergic from his parents. If he is destined to be allergic to milk, average or even small amounts will cause symptoms just as well as the ingestion of large quantities. Approximately 15 per cent of these patients were still unable to tolerate milk from one to five years later. Many others continued a dislike for milk or milk products. Clein[10] has shown that almost every one of these allergic infants will have symptoms of major allergy as he grows older. Milk is the most important food allergen.[7]

All other physical, psychologic, or mechanical causes of these bizarre symptoms should be ruled out before a diagnosis of milk allergy is made. When any one or combination of the fourteen groups of symptoms are present in an infant and persist in spite of various formula changes, medicines, or other treatments, the infant should be given the benefit, without further delay, of a soy bean milk formula to replace the cow's milk. A twenty-four- to forty-eight-hour trial feeding will quickly tell whether or not milk allergy is the major factor causing the patient's symptoms. If the baby is relieved of his complaints, the diagnosis is apparent and the result will be a happy baby and mother. If he is not relieved, further study and treatment are necessary. This group includes only those who were relieved of their symptoms by removal of milk from the diet.

Allergy to other foods is usually not a problem in the first month or two because milk is usually the baby's only food at this time. He may become sensitive to other foods and vitamins in addition to milk, as they are included in his diet. Allergic symptoms may also be caused by con-

tactants and inhalants such as dust, wool, feathers, powders, oils, animals, and fuzzy toys. If present, in these babies, they were minor factors and did not materially influence the course of the symptoms. Milk was the dominant allergen!

Some mothers still insist that their child must drink a quart of milk a day because "it is good for him." This may be true in many instances, but can be harmful if the child has any degree of sensitivity to milk.

SUMMARY

1. This is a clinical study of 140 infants allergic to cow's milk.

2. Milk allergy in infants is more common than generally recognized and may cause a variety of symptoms.

3. Fourteen different and often unrelated groups of symptoms were analyzed. The type and severity of symptoms varied with the individual sensitivity of the patient as well as the tissue or organ affected.

4. Complete relief was obtained by avoidance of cow's milk and substitution of soy milk.

5. Most babies were able to tolerate milk after abstaining for three to four months. Fifteen per cent were still unable to tolerate milk after one year of age.

6. All individuals whose symptoms are suspected of being due to milk allergy should have the benefit of a milk-free diet and a twenty-four- to forty-eight-hour trial with soy milk substitute.

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SERUM PROTEIN VALUES IN INFANTS FED SOYA-BEAN MILK

(Continued from Page 194)

In cases R. J. and T. N., electrophoretic studies failed to reveal a difference in the sera of subjects despite the fact that after three months, R. J. was on a vegetable "milk," and T.N. on cow's milk.

CONCLUSION

1. Vegetable proteins in the form of soy-bean "milk" were the sole source of proteins for the first three months of life.
2. Normal protein values were noted in the infants under study.
3. Growth and development were not disturbed.

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THE EFFECT OF ANTIHISTAMINE MEDICATION ON THE TUBERCULIN REACTION IN ADULTS

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THE ability of the antihistaminic drugs to inhibit the immediate cutaneous reaction (wheal type) produced by the injection of histamine, or by the antigen-reagin interreaction, induced many investigators to study its effects upon the delayed cutaneous reactions (tuberculin type).

Bouquet[1] tested the action of certain antihistaminic compounds on the intradermal tuberculin reaction in guinea pigs and was unable to find any inhibiting effect. Sarber,[9] administering Benadryl subcutaneously in a dose of 50 mg per kg to thirty tuberculin-sensitized guinea pigs, concluded that, in adequate dosage levels, it causes a reduction in the tuberculin skin reaction and markedly reduces the incidence of local necrosis. On the basis of these findings, Sarber states that it is important to determine whether an individual being tested is receiving any antihistaminic compounds at the time of tuberculin testing, before correct interpretation of a negative reading can safely be made. Breton[2] was the first to report a decrease in reaction intensity following the administration of Antergan. Criep et al[3] found no effect of Pyribenzamine on the tuberculin reaction even when the same antihistamine was given intradermally and the tuberculin was injected over the same site a few hours later. Judd and Henderson[7] employed antihistamines (Pyribenzamine, Benadryl, Thephorin, Neohetramine) in a series of thirty adult patients with various types of tuberculosis, in whom were studied the effects both on the Mantoux test and on the tuberculous lesions. Patients were started on 50 mg of the antihistamine three times daily. The dose was increased to 300 to 400 mg per day, as tolerated. The highest daily dose given any patient was 500 mg, and the longest period of administration was seven months. When 500 mg of the drug are given for six months, with pulmonary and other forms of tuberculosis, one begins to see the results that cannot possibly be obtained by employing 60 mg for four days. In thirty of the thirty-four cases reported, the Mantoux (using PPD, first strength) was converted gradually to negative and remained negative, except for a few instances, for the duration of the antihistamine therapy. All skin tests returned positive within four weeks after medication was discontinued. Some very interesting effects on pulmonary exudative lesions, some quite dramatic, were also demonstrated.

Friedman and Silverman[4] reported that Pyribenzamine in oral doses

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Presented at the First Congress Ibero-Latino-Americano de Dermatologia, Rio de Janeiro, September, 1950.

Neo-Antergan used in this work was supplied through the courtesy of Rhodia Chemical Co.

of 60 mg (forty-three children) or 240 mg (ten children) daily for four days had no effects on the tuberculin reaction. It is concluded that in routine tuberculin testing one need not be concerned as to whether the patient is receiving Pyribenzamine or any other antihistamine medication, during four days, and that the observations presented are in agreement with the belief that a basic difference exists between tuberculin-allergy and tuberculo-anaphylaxis.

Kending et al[8] reported that the administration of Antistine and Pyribenzamine by mouth produces no change in the skin reaction of the tuberculin patch test. Graub and Barrist,[5] studying the effect of Benadryl 50 mg every hour hours during twenty-four hours, upon the tuberculin reaction in eighty-seven patients, using 0.1 mg of PPD, first strength, intradermally, concluded that the area of induration was diminished more than 25 sq mm in five patients, while the remaining nineteen patients showed no appreciable change. Ten additional patients were given Neo-Antergan during the first test period instead of the second. It was found that in eight of these patients the size of the indurated area following the first injection of PPD was more than 25 sq mm smaller. The authors recommended that the skin reactivity should not be attempted when antihistaminic drugs are being administered.

In the work we studied the effects of Neo-Antergan upon the tuberculin reaction of thirty adult patients.

OBSERVATIONS

Thirty white adult patients from the Clinic of Dermatology were chosen for this study. Their tuberculin reactions were positive forty-eight hours after the injection of 0.1 mg of O.T. in the ventral surface of the forearm. The diameters of the areas of induration were measured at the end of forty-eight hours. Three days after this control test, the patients were given, by mouth, 300 mg of Neo-Antergan divided into three doses of 100 mg, during twenty-one consecutive days. After this period, without suspending the drug, all patients received another intradermal test of 0.1 mg of O.T. in the same forearm. The reactions were read and registered, as the former, forty-eight hours after the injection. The solutions of O.T. were freshly prepared.

RESULTS AND COMMENTS

Our results are condensed in Table I. As one can see, the drug used did not change the intensity of the skin induration of the tuberculin reaction, even after the administration of 300 mg for twenty-one days. The reaction showed, in all patients, diameters very similar to those obtained before the treatment with Neo-Antergan.

The criticism by Henderson[6] of Friedman and Silverman's results, calling attention to the importance of adequate time and dosage of the antihistamine treatment, is directed also to our work. It is far more difficult to

TABLE I. TUBERCULIN REACTION WITH AND WITHOUT NEO-ANTERGAN

Patients	Without Neo-Antergan. Induration in mm	With Neo-Antergan, 300 mg Daily for Twenty-one Days. Induration in mm
C.J.E.	20 x 22	20 x 18
A.V.	15 x 15	14 x 16
B.M.	30 x 30	28 x 30
A.S.	22 x 18	22 x 18
A.F.S.	12 x 10	10 x 10
D.B.P.	15 x 15	15 x 12
J.O.A.B.	13 x 10	14 x 12
J.R.	10 x 10	8 x 10
J.P.S.	18 x 18	16 x 16
J.A.L.	15 x 18	15 x 15
R.T.C.	12 x 10	10 x 10
M.N.	10 x 10	10 x 10
C.S.	10 x 8	10 x 10
S.A.V.	13 x 12	14 x 10
A.J.S.R.	12 x 12	10 x 12
W.A.C.	12 x 10	10 x 10
G.J.E.	10 x 12	10 x 10
J.S.	15 x 15	15 x 15
W.R.	10 x 10	10 x 12
J.A.L.	15 x 15	14 x 14
P.A.M.	20 x 18	20 x 20
T.J.P.	18 x 18	16 x 18
G.D.	15 x 16	15 x 15
C.M.	15 x 17	15 x 15
A.R.T.	15 x 15	12 x 14
D.M.L.	22 x 20	20 x 20
G.R.	30 x 28	24 x 24
N.M.O.L.	15 x 15	14 x 14
C.G.A.	18 x 18	18 x 16
C.B.M.	17 x 16	10 x 16

conciliate our results with those obtained by Graub and Barrist.[5] We are continuing our studies, and we cannot change our opinion about the inefficacy of Neo-Antergan upon the tuberculin reaction.

It seems that a basic difference really exists between tuberculin and urticarial reactions. One should also conclude that in routine tuberculin testing one need not be concerned as to whether the patient is receiving Neo-Antergan even during twenty-one consecutive days.

SUMMARY

1. Neo-Antergan, 300 mg daily for twenty-one days, produced no effect on the tuberculin reaction of thirty adult patients.

2. It is concluded that in routine tuberculin testing one need not be concerned as to whether the patient is receiving Neo-Antergan even during twenty-one days.

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(Continued on Page 278)

CLINICAL OBSERVATIONS WITH CLOPANE IN ASTHMA, HAY FEVER AND ALLERGIC RHINITIS

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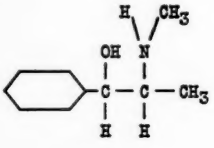
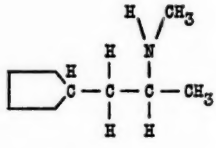
ACCORDING to Chen,[1] Clopane is more potent as a vasoconstrictor than ephedrine. Because of this property it would seem of value in diseases such as bronchial asthma, hay fever and allergic rhinitis. In bronchial asthma it could be used as a substitute for ephedrine. Reports on ephedrine date back to 1926, when Gaarde and Maytum[2,3] used it in fifty cases of hay fever. They reported complete relief in twenty-six instances and partial relief in twelve more cases. Twelve patients could not tolerate ephedrine because of the side reactions. It is now common knowledge that ephedrine produces a series of undesirable side reactions when taken therapeutically. These include nervousness, tremor, sweating, sleeplessness, nausea and palpitations. Therefore, Clopane was tried in the hope that there would be fewer side reactions. The following is a report on thirty-six cases of asthma and forty-five cases of hay fever and allergic rhinitis treated with Clopane.

Pharmacologically, Clopane, when compared to ephedrine, has the same duration of action but a greater stimulating effect on the sympathetic nervous system and about one-fourth as much on the central nervous and cardiovascular systems. Chen and Swanson[4] showed that the presence of the benzene ring in the formula of ephedrine was not necessary for its vasoconstricting action, since straight chain amines can exert such an effect. Clopane is a cyclopentylamine. The comparative formulas are shown below.



Ephedrine



Clopane

CLINICAL REPORT

Thirty-six patients suffering from bronchial asthma of various degrees took Clopane. Some were also on a desensitization program and/or potassium iodide. No other medication was prescribed. The dosage of Clopane varied from 25 mg three times a day to 100 mg four times a day. The action of the drug became manifest in an average of twenty to thirty minutes, and lasted three to four hours. Twenty-four patients showed satisfactory to good relief. As expected, those mildly asthmatic showed the best re-

From the Department of Medicine, Marshfield Clinic and St. Joseph's Hospital, Marshfield, Wisconsin. Read before the Wood County Medical Society, January, 1950.
Clopane supplied by Eli Lilly and Company.

sults, but a few with severe symptoms also experienced relief because they were able to take more of this drug without side reactions. Seven asthmatic patients have taken Clopane daily for a year without any apparent ill effects. In twelve instances Clopane was discontinued because there was no apparent relief.

Fourteen patients were able to compare Clopane with previous experience with ephedrine or ephedrine combinations. Eight felt it was equivalent; six thought the relief was not as good, although two of these preferred it because of few side reactions. Those asthmatic patients who preferred Clopane felt they were better able to carry on their work as a result of the high tolerance. The most pronounced side reaction was a dull headache which occurred in four patients. There was slight dizziness in four, and one male complained of some urinary retention.

Forty-five patients with hay fever or allergic rhinitis received Clopane in doses of 25 to 50 mg two or three times daily. It was noted that much less Clopane was needed for relief of these conditions than in asthma. All except five experienced satisfactory relief of nasal congestion by diminution of secretions and constriction of the swollen and edematous turbinates. As it is known that antihistaminic drugs diminish secretions of the mucosa but do not constrict the swollen turbinates, a trial of Clopane plus an antihistamine was made. A capsule containing 12.5 mg of Clopane and 25 mg of Histadyl was used three times a day. It is believed that there is a synergistic action because of longer and more adequate relief when used together. The side effects were practically absent owing to the small doses needed for relief. An occasional slight dull headache or a light-headed feeling was reported.

CONCLUSION AND SUMMARY

The satisfactory response of twenty-four out of thirty-six asthmatics and similar relief of forty out of forty-five hay fever or allergic rhinitis patients indicates that Clopane is an active vasoconstrictor and a valuable addition to the drug treatment of these diseases. Its use practically eliminated the side effects usually found with ephedrine. Therefore, when side effects from ephedrine interfere with working, Clopane might be the drug of choice. A combination of Clopane and an antihistaminic drug appeared of value in treating hay fever and allergic rhinitis. As a result, Clopane will find a place in the drug treatment of these conditions because of its efficacy and fewer side effects.

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AN UNUSUAL CASE OF MULTIPLE DERMAL ALLERGIES

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IT is a common experience to see the same syndrome elicited by sensitization to several antigens, as, for instance, bronchial asthma caused in the same patient by several antigenically unrelated pollens, house dust, et cetera. It is also by no means rare to see various types of sensitization in the same patient arise, as, for instance, bronchial asthma caused by inhalants and urticaria caused by food. However, it is exceptional to find the same shock organ, for example, the skin, respond to multiple antigens in different ways. It appears therefore worthwhile to record a case in which three different kinds of dermal hypersensitivity could be traced to different sensitizations, and for which we were fortunate enough to establish the causative agents and thus to open the road to rational therapeutic procedures.

CASE REPORT

R. I., a seven-year-old adopted child of unknown family background, was first seen on August 12, 1949. The main complaint was a chronic affection of the popliteal space of the right knee extending to the dorsal side of the right thigh and right lower leg. There was severe itching and oozing, so strong that about thirty yards of gauze were used every second day for dressings. Large amounts of an ointment of unknown composition had been used to control the itching, but without success. Several physicians, including dermatologists, had been consulted. Food evidently had been considered as an etiological factor, for the child when first seen was on a diet which severely restricted his food intake both in variety and in quantity. This affection had existed since 1945. It appeared to become worse in spring and to improve in late fall.

Furthermore, there was a history of an affection of both forearms, which was described as "hives" and which came and disappeared at irregular intervals.

The foster mother had also observed a scaling of the palmar surfaces of both hands.

Finally, there was a mucous discharge of both eyes and continuous tearing, which was stated as being present only during the warm weather between spring and late fall. This condition, too, had started four years ago.

Objective Findings.—The child was in poor nutritional state, his weight being 45 pounds and his height 46 inches.

The internal organs showed no deviation from the normal.

Urine Examination: Albumin and sugar, negative. Acetone, 3 plus. Sediment contained a few leukocytes.

Blood Examination: Leukocytes, 16,100. Red blood cells, 5,080,000. Hemoglobin, 95.4 per cent (14.8 gm). Neutrophiles, 81 per cent (segments, 80; rod, 1); lymphocytes, 18 per cent; monocytes, 1 per cent.

Both eyes were tearing and showed a colorless mucous discharge.

Scaling was seen on the palmar sufaces of both hands.

All the pollens, house dust and feathers were prepared by the author. We are indebted to Dr. A. Kibrick of the Bronx Hospital for his aid in the determination of the nitrogen content of the extracts used. The food and other extracts were purchased from the Lederle Laboratories.

There was a spotty irregular rash, with whitish raised centers about 0.4 cm in width, on both sides of the forearms. Subsequent visits showed that the rash came and went at unpredictable intervals.

In the region of the right popliteal space and extending from the middle of the right thigh to the middle of the right leg, there was an area of erythema and induration which was oozing copiously; it had a foul odor and showed numerous excoriations.

Intradermal tests were done as follows:

Inhalants.—
House Dust (Concentrate) moderate reaction.
Mixed Ragweeds: 0.0001; 0.001; 0.01....negative.
0.1....slight 0.2....moderate.
Timothy: 0.0001; 0.001; 0.01....negative.
0.1....slight 0.2....moderate.
Plantain and Trees (Oak and Birch); 0.001; 0.01; 0.1; 0.2....negative.
Rabbit Epid., .001, Dog Epid., .001, Cat Epid., .001, Horse Epid., .001, Sheep's Wool, .001, Orris Root, .001, Cottonseed, .001, Kapok, .001, Flaxseed, .001, Fish (glue), .001, Silkworm, .001....negative.
Goat Epid., .01, Feathers, .1, Tobacco, 1:10, Pyrethrum, 1:100....negative.
(All concentrations mg total N/ml).

Food Extracts.—
Beef 1:10....marked.
Rye, Corn, Spinach, Ginger, 1:10....moderate.
All other foods. Egg White, .001; Milk, 1:10; Lamb, 1:10; Potato, 1:10; Chicken, 1:10; Orange, 1:10; Lima Bean, 1:10; Green Pea, 1:10....negative.

Course.—On the basis of these data, a diagnosis was made of (1) vernal catarrh (allergic conjunctivitis), (2) atopic eczema, (3) urticaria, (4) affection of the hand of a doubtful nature.

Treatment was started for the one affection for which the causative factor could be ascertained, namely, the vernal catarrh. A schedule was adopted as routinely used in our clinic and office, which approximated the procedure as recommended, for instance, by Vaughan,[4] starting with subcutaneous injections of mixed ragweed, plantain, timothy and trees (oak and birch) extracts in dosage of 10 to 20 (Noon) pollen units each, increasing the doses by 10 to 20 units each time and giving treatment daily, every second day, et cetera. House dust was added, starting with 0.05 ml of the 1:50 dilution and increasing by 0.05 ml of the same concentration. Histamine acid phosphate also was given in small doses, 0.05 ml of the 1:100,000 dilution, increasing by steps of 0.05 ml. No medication was used on the skin during this period. Calcium gluconate (Flint) effervescent about 100 grains daily was the only medication taken internally. Plantain and trees (oak and birch) were added according to our experience that sometimes antigens are involved that do not give positive skin tests (see, for instance, Marton[1]).

Improvement of the eye symptoms became apparent after a few treatments. The conjunctivitis completely disappeared at the fourth week and never recurred.

This improvement was closely paralleled by a regression of the dermatitis of the knee. The oozing stopped after three days, so that no dressings were needed. As a matter of fact, the intended photographing of the lesions had to be abandoned because the affection had become entirely unobstrusive at the time when the necessary arrangements had been made.

At this point, when an average dose of 200 pollen units for each of the pollens had been reached after ten treatments, which happened to be at the height of the rag-

weed season in New York during the first week in September, a recurrence of the rash in the right popliteal space was noted. We reasoned that this might be the expression of an overdosage, in other words an overloading of the circulation with antigen, which the body at this point was not (yet) able to neutralize. Correspondingly, we reduced the dosage of all antigens to about one-fourth of the dose we had reached, and we had the satisfaction of seeing the healing proceeding without further interruption. After a total period of four weeks the affected skin area had regained a completely normal aspect with no pigmentation. No recurrence has been noted to date.

During this period, the child gained 5 pounds in weight. Altogether the child's weight increased by 20 pounds within a seven-month period. It should be noted that all dietary restrictions had been removed at the beginning of the treatment. The patient is still on a free diet with the exceptions explained in the following paragraphs.

During the period of treatment with the inhalants, the urticaria had not improved. We had, therefore, to look for different antigenic agents in order to obtain information on the causation of this affection. Of the food extracts that we had used in testing, beef attracted our attention because of its nutritional importance and because it was the only one that gave a strong reaction. It was recommended that beef be withheld from the diet for ten days. The urticaria promptly subsided. A confirmatory test was made by restoring beef to the diet, and the hives reappeared. From this time on, beef was completely eliminated from the diet, with no recurrence of urticaria.

There remained the minor affection of the hands. The child, living with Italian foster parents, frequently ate cheeses such as Parmesan, Gorgonzola, and Roquefort, which were rich in molds. A chance was taken, by a "long shot" trial of the effects of eliminating these cheeses. Within a week the affection of the hands cleared and has not recurred. A retrial has not been attempted at this writing.

DISCUSSION

Besides the allergic conjunctivitis, our patient showed three different skin affections, namely, (1) atopic eczema, caused by the same inhalant antigens as the conjunctivitis (vernal catarrh), (2) urticaria, caused by beef, (3) a scaling dermatosis of the palms, presumed to be caused by the cheese food, possibly the mold antigens contained in the cheeses.

Atopic eczema caused by allergy to inhalants has been repeatedly reported as for instance by Rowe[2] and Tuft.[3] The latter offered, as far as we can see, the first conclusive evidence for this occurrence. From the scanty data in the literature, it would appear that inhalants are involved as etiological agents of atopic dermatitis only in rare cases. From our own experience we are inclined to suspect that this may not be quite as rare as supposed, but may perhaps often escape detection. In our clinic and private practice which concentrates on the treatment of allergies of the respiratory tract, we had occasion to see many cases of a combination of asthma or hay fever with allergic dermatitis, in which systemic (immunizing) treatments with agents causing the respiratory allergies resulted in the clearing up of long-standing dermatoses. For this reason, we would like to call attention to this particular aspect of the case presented here.

(Continued on Page 279)

ALLERGY IN OTOLOGY

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THE otologist is frequently confronted with cases of hearing difficulty which do not fit well into the usual categories for analysis. Of these patients who were obviously allergic and in whom there were other general allergic symptoms, there seemed to be a definite improvement in hearing when they were placed under allergic management. With this stimulus of improved hearing our interest was led to consider allergy as a factor to be followed in cases of deafness or declining hearing, especially if any changes of an allergic nature were in evidence. We noted that some types of deafness seemed to be aggravated by allergy and that some ear pathologies have superimposed on them an allergic situation. Many children who had had tonsillectomies and adenoidectomies because of hearing difficulties were greatly improved immediately following the operation. Some later relapsed into the same hearing difficulties and then were found to be allergic. In an attempt to evaluate these findings and deductions we were led to study an entire group of cases of this type. The most exaggerated symptom that we noted is the variability of both the presence of hearing changes and their intensity from day to day and hour to hour. The following symptoms in these cases were noted to be:

1. Fullness in one or both ears.
2. Loss of hearing or dullness of hearing.
3. Deep, dull pain in the ear.
4. Itching in back of the nose and "between the nose and the ear."
5. Tinnitus, vertigo, and nausea.
6. Tightening and drawing in the ear.
7. Deep burning in the ear.
8. Wide differentiation between the healing time of one type of middle ear infection as against some others.

DIAGNOSIS

If a patient presents himself with a change in his hearing that is variable and has some of the above mentioned symptoms, an audiogram—and the patient's feelings as far as the ears are concerned—are compared with an audiogram made twenty minutes after a hypodermic injection of half the therapeutic dose of epinephrine. If there is a change in the hearing and a change in the feeling of the patient's ears subjectively, we can consider the allergic influence to be of enough importance to warrant investigation from this standpoint. We may also find a positive nasal secretion eosinophilia or blood eosinophilia confirmatory.

Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

Pathologically one frequently sees eustachian tube edema or edema around the eustachian tube tip as viewed through a nasopharyngoscope and middle ear edema, i.e., swelling of the mucous membrane of the middle ear.

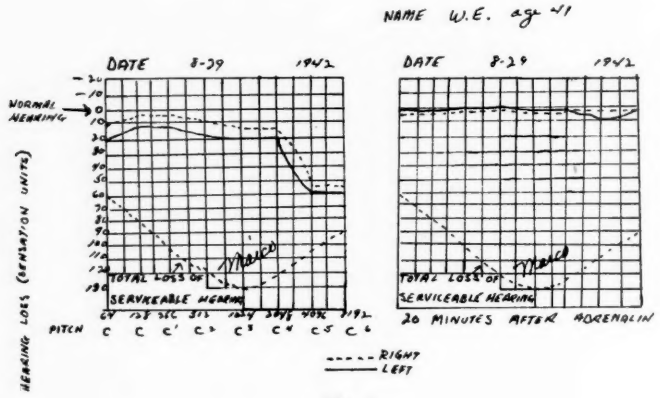

Fig. 1.

It is not uncommon to note that after myringotomy with a very small amount of secretion there will be a pouching out of swollen mucous membrane through the myringotomy opening. It may be deduced, therefore, that middle ear edema is present. The dull appearance of the drums is noted in these cases that are relatively acute. However, one must be very critical and constantly on guard not to be misled by appearance and findings. The findings and audiometric changes, I believe, justify a conclusion after therapeutic results have been achieved and analyzed.

The audiograms in Figures 1 and 2 are of two interesting cases.

Case 1.—W. E., aged forty-one, had a reduction in hearing that had been noticed for some time, and the first audiogram (Fig. 1) shows that he had a considerable loss in the amount of *hearing in high tones* which was relieved in twenty minutes by the injection of 8 mm of epinephrine subcutaneously. This patient was sensitive to tobacco, and on investigation we found that each time he smoked too much he noticed a rather abrupt change in his hearing which lasted one or two days before he recovered.

Case 2.—In C. G., aged ten, the nose was open, and he was entirely free of symptoms, but there was a positive nasal smear for eosinophils and the epinephrine test was highly positive for allergic ears. The hearing rapidly came to normal (Fig. 2) after the allergens to which he was found sensitive were excluded.

In our experience foods, tobacco, dust, serums, penicillin, streptomycin, and brucellar infections have been noted to be the etiology of these same changes. Involvement of the middle ear with hearing difficulties from

infections should also be considered in diagnosis. Recently in otology our attention has been directed to the allergic processes in the middle ear that are of a serous nature. To investigators such as Dean, Proetz, Hansel, Dohlman, and Koch—to mention only a few—goes the honor of establishing

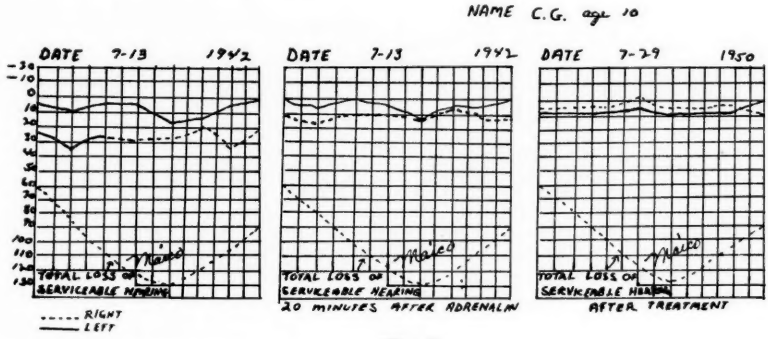

Fig. 2.

the great importance of a high eosinophilia count in the secretion coming from the middle ears as evidence of an allergic involvement, in the same way as finding many eosinophils in a nasal infection indicates an allergy.

It is common knowledge that many acute and chronic middle ear infections develop in an insidious way without any demonstrable connection with infections or nasopharyngeal abnormalities. In these cases with perforations, a normal air cell system and a mucoid secretion, bone infection of the mastoid is not probable. This same finding of mucoid secretion and continued discharge full of eosinophils is frequently seen in ears radically operated upon. These discharging ears in the past had been treated in a stereotyped way with rinsing, alcohol drops, insufflation of boric and iodine powder, et cetera, and finally they were either considered as failures in treatment or an operation was performed to eradicate the origin of the infectious process. These operations were often of only transient value, for they did not take into account the allergic factor in the middle ear discharges and mucous membrane changes. During the last five or six years, therefore, more attention has been directed to the study of the secretions from draining ears in an attempt to determine the etiology of the process involved in the maintenance of this persistent secretion with changes in hearing. A radical mastoid cavity may not heal quickly and may remain moist. If the secretion is full of eosinophils and proper allergic management is instituted, the ears frequently clear up very promptly. So the classification of all ear secretions has differentiated middle ear involvement into eosinophilic and aeosinophilic affections. Bacteria may be secondary or superimposed on the process. I believe this is of much more frequent occurrence than we have thought until the recent researches.

Albrecht has found that 86 per cent of the eosinophilic chronic otitic ears are in patients or children who had been bottle fed, indicating that one must think of milk sensitivity in these cases, as this is a much greater percentage than ordinarily one would expect. He expounded as a theory that these patients were locally sensitized by regurgitating the foreign protein of milk through the eustachian tubes into the middle ear, the eustachian tube being quite straight and open in young children, making this phenomenon a very easy occurrence.

Dohlman noted that certain ear conditions were associated with other allergic symptoms such as asthma and gastrointestinal disturbances. He further confirmed Albrecht's theory, especially in children who are hereditarily predisposed to allergic diseases and who were bottle fed, by pointing out that almost all of these cases were massed in certain families with these predisposing factors in their histories.

It is very important to secure eosinophilic smears from the secretions of chronic middle ear infections, but they are more easily secured during and especially after an acute exacerbation. There is an hereditary factor that must be considered in discharging ears of chronic nature, both in the eosinophilic and aeosinophilic cases. Where it is demonstrated that a patient is hereditarily predisposed to the allergic diseases, one must make repeated studies to bring out a positive eosinophilic finding. When there is an acute exacerbation, as in a cold, there is an increase in the bacteria and a swing to the neutrophilic side in the smears; but as the inflammatory situation balances itself it returns to a predominance of eosinophils, so that repeated studies must be made in order to differentiate the cases for further allergic studies. To Dohlman must go the thanks of otologists for his investigations which have called our attention to these allergic infections of the middle ear. In an accompanying nasal allergy an allergic cause for the inflammation must always be expected.

APPEARANCE OF THE MIDDLE EAR

The mucosa of the middle ear was found to be edematous in all cases where it could be inspected. In most of the cases the swelling was pronounced, and in the acute bacterial stages the mucosa was reddened. As the inflammation subsided, the mucosa was pale pink or violet. This characteristic appearance of the mucosa was simultaneous with the appearance of eosinophils in the secretion of the eosinophilic cases.

We have frequently observed that in a case of an acute infection with fever and excessive discharge, either acute or chronic, neutrophils predominate. As the infection subsides in the eosinophilic cases, there comes an overwhelming increase in the eosinophils as the neutrophils decline, so that repeated studies of the secretions of the ears with a tendency to chronicity must be made with every acute exacerbation, in addition to bacterial studies for possible specific antibiotic and autovaccine therapy.

Some characteristics differentiating aeosinophilic and eosinophilic chronic

otitis are that the aeosinophilic are much more difficult to treat, are much less likely to respond, and tend more to produce cholesteatoma and to require radical surgery.

TREATMENT

In the management of these cases one must call attention to the sensitizing effect of certain medications, sulfathiazol powder being a classical example. With this in mind we have reduced the treatment in proven cases of chronic eosinophilic otitis to extreme cleanliness, using lavage only when the secretion is very heavy, and then with boiled water only, with the addition of allergic management as indicated. If no desensitizing or avoidance factors could be uncovered, an autovaccine made from the secretions of the middle ear has had a beneficial effect. This is done because of the feeling that the bacteria that originally started the middle ear infection may have sensitized it. If there is an accompanying allergic nose, intensive active treatment to the nose along prescribed lines is indicated.

CONCLUSION

Allergic hearing difficulties are relatively easy to diagnose and can be very satisfactorily treated by purely allergic methods with attention to nasal difficulties, either allergic or infectious. The aeosinophilic chronic infections are much easier to treat and much less likely to become complicated than the eosinophilic, which are more chronic in their reactions. They require much more intensive and long-drawn-out treatment, and the addition of proper allergic management is of high therapeutic value.

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TREATMENT OF RHUS DERMATITIS
A Clinical Comparison of Two Injectable Antigens

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RHUS dermatitis is a common problem to the general practitioner, but too frequently the therapeutic results are disappointing. Even the newer systemic antihistamines and antipruritic agents provide only partial relief from the itching. Local applications provide only temporary relief, and, of course, have no effect upon the generalized systemic reaction of the patient. Densensitization with injectable antigens has long been a favored method for treating this condition.

Two general types of antigen are available. In one, the oleo-resin is dissolved in oil; in the other, alcohol is the solvent. This study was undertaken in an attempt to compare the relative efficacy of these two types of antigen.

Twenty-six consecutive patients with rhus (poison sumac) dermatitis were treated. All of these came from a university forestry camp in this area. The following arbitrary classification of the severity of the dermatitis was used: *mild:* pruritus, erythema; *moderate:* pruritus, erythema, and edema; *severe:* pruritus, erythema, edema and vesicle formation; *very severe:* pruritus, erythema, edema, vesicle formation, severe systemic reaction and total incapacity. Six cases, mild to moderate in severity, were selected as controls. These patients used lotions or Surfacaine as needed, and received Benadryl 25 mg every four hours. Most of these obtained temporary subjective relief, but the treatment had no apparent effect on the course of the dermatitis. The remaining twenty patients received injections of antigen. Alternate cases were given aqueous-alcoholic antigen (Rhus Tox Antigen*); the others received the extract in oil (Ivyol†). The manufacturer's dosage recommendation was followed in each instance (Rhus Tox Antigen 1 cc; Ivyol 0.5 cc.). The chart records the relative effectiveness of these two preparations (Table I).

To further evaluate the results of therapy a numerical grade was assigned as follows: relief obtained in twelve to twenty-four hours, 4 points; relief in twenty-four to thirty-six hours, 3 points; relief in thirty-six to forty-eight hours, 2; relief only after forty-eight hours, 1; little or no improvement, unsatisfactory, 0. On this basis the relative efficacy can be determined by adding the points. For Rhus Tox Antigen, the total is 37, while Ivyol scored only 17 points.

One of the striking features observed in the use of Rhus Tox Antigen was the rapidity with which relief was obtained. Some showed very decided improvement within eight to twelve hours.

*Manufactured by Mulford Colloid Laboratories, Philadelphia, Pennsylvania.
†Manufactured by Sharp and Dohme, Inc., Philadelphia, Pennsylvania.

TABLE I

Case	Patient	Age	Severity of Dermatitis	Preparation and Dose	Total Number Daily Injections	Results
1	J. B.	23	severe	Rhus Tox Antigen 1 cc	4	excellent
2	P. A.	22	severe	Ivyol 0.5 cc	3	good
3	C. H.	21	severe	Rhus Tox Antigen 1 cc	3	excellent
4	R. F.	24	severe	Ivyol 0.5 cc	4	fair
5	G. W.	25	severe	Rhus Tox Antigen 1 cc	3	excellent
6	R. W.	29	severe	Ivyol 0.5 cc	5	good
7	C. J.	25	severe	Rhus Tox Antigen 1 cc	4	excellent
8	M. R.	23	severe	Ivyol 0.5 cc	3	unsatisfactory
9	W. C.	20	severe	Rhus Tox Antigen 1 cc	3	excellent
10	L. P.	21	severe	Ivyol 0.5 cc	5	unsatisfactory
11	F. D.	18	moderate	Rhus Tox Antigen 1 cc	2	excellent
12	H. S.	28	moderate	Ivyol 0.5 cc	4	fair
13	J. E.	30	very severe	Rhus Tox Antigen 1 cc	7	poor
14	R. G.	23	very severe	Ivyol 0.5 cc	2	unsatisfactory
15	H. G.	21	mild	Rhus Tox Antigen 1 cc	5	excellent
16	C. S.	26	mild	Ivyol 0.5 cc	4	fair
17	C. J.	22	very severe	Rhus Tox Antigen 1 cc	4 1	excellent
18	B. J.	27	moderate	Ivyol 0.5 cc		good
19	P. A.	24	very severe	Rhus Tox Antigen 1 cc	2 4	excellent
20	J. A.	22	severe	Ivyol 0.5 cc		fair

SUMMARY

Twenty-six patients with rhus (poison sumac) dermatitis were studied.

Six mild cases were treated with local applications and antihistamines. This therapy had no apparent effect on the course of the dermatitis.

Ten patients received injections of the specific oleoresin in oil. The average response was fair.

Ten patients received injections of an aqueous-alcoholic solution of the antigen. This form of therapy proved far superior to the other methods of treating the dermatitis.

SCOLIOSIS OF THE SPINE AND ASTHMA

(Continued from Page 189)

lumbar region which causes a stimulation of the delicate pre-ganglionic fibers is suggested as a cause of asthma.

Three cases of asthma with dorsolumbar scoliosis are reported where complete cure followed the restoration of the spine to its normal position.

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CORRELATION OF REACTIONS TO SCRATCH AND PATCH TESTS IN PATIENTS WITH ATOPIC DERMATITIS

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THIS study was undertaken because previous investigations[2] have shown that the urticarial reactions to scratch tests with human dander in patients with atopic dermatitis are, in a large percentage of cases, accompanied by characteristic atopic reactions to patch tests with the dander. The question arises, to what extent do atopic reactions to patch tests with inhalants and foods accompany the urticarial reactions to scratch tests with these substances?

Twenty patients with atopic dermatitis, aged six months to twenty-eight years, were tested with dwarf ragweed pollen, blue grass pollen, human dander and hen's egg. For the scratch tests 2 per cent extracts in 50 per cent glycerine were used. For the patch tests the pollens and dander were mixed with sufficient petrolatum to make a thick paste. Egg white and glycerine, equal parts, were used for the patch tests with egg. Patches were applied on normal, unaltered skin and also on skin previously scratched once slightly with a needle. They remained in position for two days, and the readings were made one day after removal of the patches. Petrolatum and glycerine applied to scratches were employed as controls.

RESULTS

The reactions occurred as follows:

1. *Ragweed Pollen.*—Seventeen patients gave urticarial reactions. Two of these gave atopic reactions to patch tests on normal skin, and four gave such reactions to patch tests on scarified skin.

2. *Blue Grass Pollen.*—Seven patients gave urticarial reactions. None gave atopic reactions to patch tests on normal skin, but one gave such a reaction to patch tests on scarified skin.

3. *Human Dander.*—Thirteen patients gave urticarial reactions. Six gave atopic reactions to patch tests on normal skin. These were chiefly young children. Seventeen gave such reactions to patch tests on scarified skin. Four of the latter were young children who gave negative urticarial reactions to the dander but positive reactions to patch tests.

4. *Hen's Egg.*—Seven patients gave urticarial reactions. One gave an atopic reaction to patch tests on normal skin and also on scarified skin.

From the Departments of Medicine and of Bacteriology and Immunology, University of Louisville School of Medicine.

TABLE I

Case No.	Age (yrs.)	Allergen	Scratch	Patch on Normal	Patch on Scratch	Blank on Scratch
1	½	Dw. Ragweed	−	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	−	+++	+++	−
		Egg	++++	++++	++++	−
2	7/12	Dw. Ragweed	−	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	−	+++	+++	−
		Egg	+++	−	−	−
3	10/12	Dw. Ragweed	++	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	−	+	++	−
		Egg	++++	−	−	−
4	3	Dw. Ragweed	+++	±	+++	−
		Blue Grass	−	−	−	−
		Human Dander	−	+++	+++	−
		Egg	++++	−	−	−
5	8	Dw. Ragweed	+++	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	+	±	+++	−
		Egg	−	−	−	−
6	13	Dw. Ragweed	++++	++	+++	−
		Blue Grass	+++	−	±	−
		Human Dander	++	+	++	−
		Egg	−	−	−	−
7	14	Dw. Ragweed	+++	−	−	−
		Blue Grass	+++	−	−	−
		Human Dander	+	−	+	−
		Egg	−	−	−	−
8	15	Dw. Ragweed	+++	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	++	−	++	−
		Egg	−	−	−	−
9	18	Dw. Ragweed	++	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	±	−	+	−
		Egg	−	−	−	−
10	18	Dw. Ragweed	++++	−	++	−
		Blue Grass	−	−	−	−
		Human Dander	+	±	++	−
		Egg	++++	−	−	−
11	18	Dw. Ragweed	+++	−	−	−
		Blue Grass	++	−	−	−
		Human Dander	±	−	++	−
		Egg	−	−	−	−
12	19	Dw. Ragweed	±	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	++	+	+++	−
		Egg	−	−	−	−
13	22	Dw. Ragweed	++	−	−	−
		Blue Grass	+++	−	−	−
		Human Dander	++	−	+	−
		Egg	−	−	−	−
14	23	Dw. Ragweed	++++	++++	++++	−
		Blue Grass	++++	±	+	−
		Human Dander	±	−	±	−
		Egg	−	−	−	−
15	23	Dw. Ragweed	++++	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	++	−	−	−
		Egg	++	−	−	−
16	24	Dw. Ragweed	++	−	−	−
		Blue Grass	+	−	−	−
		Human Dander	+	−	++	−
		Egg	−	−	−	−

TABLE I—CONTINUED

Case No.	Age (yrs.)	Allergen	Scratch	Patch on Normal	Patch on Scratch	Blank on Scratch
17	25	Dw. Ragweed	++++	−	−	−
		Blue Grass	+++	−	−	−
		Human Dander	++	−	+++	−
		Egg	−	−	−	−
18	25	Dw. Ragweed	+++	−	±	−
		Blue Grass	−	−	−	−
		Human Dander	++	−	+	−
		Egg	−	−	−	−
19	27	Dw. Ragweed	+	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	+++	−	−	−
		Egg	−	−	−	−
20	28	Dw. Ragweed	++++	−	−	−
		Blue Grass	−	−	−	−
		Human Dander	++	−	++++	−
		Egg	+++	−	−	−

The reactions to patch tests with human dander occur much more frequently than do such reactions to the other substances tested. These results are shown in Table I.

DISCUSSION

The simplest and most obvious explanation of the characteristic atopic reaction to patch tests is that this phenomenon is an allergic reaction of the atopic type occurring in a special tissue—the epidermis. This explanation is in agreement with the gross and microscopic appearance of the lesions,[3] their development and retrogression. Extending this hypothesis further to the problem of atopic dermatitis, it appears that individuals who develop atopic hypersensitiveness to foods or inhalants usually exhibit the type characterized by the urticarial reaction without the reaction to patch tests. Albert and Walzer[1] have shown that this statement holds true for a variety of foods and inhalants in cases of hay fever, asthma, and atopic dermatitis and that the incidence of reactions to patch tests with these foods and inhalants is no greater in patients with atopic dermatitis than in atopic patients without dermatitis. It should be noted that exposure to foods and inhalants is by way of the alimentary and respiratory tracts.

If we turn to the problem of allergy to human dander, we find an entirely different situation. The reactions to patch tests occur almost exclusively in patients with atopic dermatitis,[4] and the incidence of such reactions is high compared with urticarial reactions (Table I). Here it should be noted that there is a special reason for both these phenomena, namely, the fact that the allergen of human dander is present in the epidermis[5] and hence exposure is by way of the epidermis. Hypersensitiveness develops first in the epidermis; only later in life do we find the urticarial reactions of the dermis. In fact, these latter may be associated with certain clinical differences between atopic dermatitis in the adult as

compared with that in the infant, as emphasized by Sulzberger, Hill and others. The high incidence of symptoms (dermatitis) in patients allergic to human dander may be explained on the basis of this presence of the allergen in the epidermis. This fact eliminates the tremendous dilution factor which must be taken into consideration in cases in which an allergen is supposed to reach the epidermis from the alimentary or respiratory tracts by way of the blood stream, lymphatics, and intercellular tissue fluid of the epidermis. The location of the lesions as well as seasonal, climatic and other variations of the disease may be partially explained, theoretically, by assuming that such factors as thickness of epidermis, flexion and extension, rubbing, scratching and other trauma, and temperature changes, with resultant influence on the circulation of the skin, have a bearing on the quality or quantity of allergen which is able to accumulate and to penetrate in reactive concentration to the sensitive cells.

SUMMARY

Twenty patients with atopic dermatitis who gave urticarial reactions to scratch tests with one or more of the following substances: ragweed pollen, blue grass pollen, human dander, and hen's egg, were tested with these same substances by patch tests and patch-on-scratch tests in order to determine the incidence of "characteristic atopic reactions to patch tests." It was found that the incidence of such reactions was very much greater in the case of human dander than with the other substances tested. The characteristic atopic reaction to patch tests is regarded as being an allergic reaction of the atopic type in the epidermis. The high incidence of reactions to patch tests with human dander is explained on the basis of the previously demonstrated presence of the allergen of human dander in the epidermis, not only of the scalp but also of the general body surface.

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ALLERGIC PURPURA RESPONDING TO ANTIHISTAMINIC THERAPY

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PRIMARY purpuras may be due either to a deficiency of platelets in the blood or to damage of the blood vessel walls leading to the extravasation of blood into the tissues. The allergic purpuras belong to the latter group, and are further subdivided into Henoch's purpura, purpura simplex, and rheumatic purpura. Purpura simplex, the commonest of the three, consists of a petechial eruption which lasts several days, usually without constitutional reaction. Henoch's purpura is similar inasmuch as there is the petechial rash, usually associated with other constitutional symptoms such as abdominal pains, melena, hematemesis, urticaria, joint pains, and edema of joints. This syndrome was first suggested as an allergic disease by Henoch[3] in 1868 and 1874. Years later Osler[4] definitely established the allergic origin of the disease, thereby strengthening Henoch's original contention. Following this original work many other workers have reported cases of allergic purpura. In 1927 Alexander and Eyermann[1] definitely proved the connection of food allergy with purpura in nine cases of the Henoch type. In addition to the positive intradermal tests obtained they also showed that the purpuras disappeared as soon as the offending foods were withdrawn from the diet. At will they also reproduced the purpuric lesions by having their patients ingest the forbidden foods. In 1936 Diamond[2] reported purpuras in four children proven allergic to chocolate, and in 1937 Squier and Madison[5] reported cases in which the purpura disappeared dramatically after the withdrawal of the offending foods in question.

Pathologically, urticaria has been proven due to the extravasation of serum through the blood capillary walls into the tissues, producing the characteristic wheal. In the allergic purpuras the mechanism is the same except that there is the extravasation of whole blood instead of serum into the tissues. This produces the characteristic petechial lesion of purpura instead of the urticarial wheal. Therefore the difference between urticaria and purpura is due only to the degree of increased permeability of the blood vessel wall that exists at the time of the reaction. The basic explanation for the described mechanism is still obscure at this time.

CASE REPORT

A fifteen-year-old white orphaned girl with the history of onset of a purpuric rash on her extremities, back, and buttocks on February 21, 1950.

From the Allergy Clinic, Mary Immaculate Hospital.
Dr. Sacca is an Associate Fellow of The American College of Allergists.

Since she was under the jurisdiction of the New York Foundling Hospital, she was seen by their staff, and the diagnosis of toxic purpura was made. Treatment consisted of Rutin 60 mg daily, ascorbic acid 300 mg daily, and a high protein diet. Laboratory work-up at this time (February 21, 1950) was: red blood cells 4,490,000, hemoglobin 13.9 gm, white blood cells 7,500, with a differential of 72 polymorphonuclear cells, 26 lymphocytes and 2 eosinophiles. Bleeding time was 1½ minutes, and clotting time 5 minutes. Platelets were 230,000. Urinalysis was normal except for a trace of albumin.

On February 28 the patient was again seen at the New York Foundling Hospital, and at this time the eccymotic lesions had spread to the neck and face. Treatment with Rutin and ascorbic acid was continued.

On March 6 the patient was seen at the Foundling Hospital for the third time, where it was noted that the old lesions were turning brown in color. A new crop of purpuric spots was appearing among the older fading lesions. Treatment was continued as above.

On March 20 she was seen for the fourth time, and at this examination the lesions had become a very light brown in color. No new petechial areas were noted, and the patient was discharged as improved. The final diagnosis was toxic purpura, cause undetermined.

One of the authors (J. S.) first saw the patient on April 5. At this time she gave the history of having developed abdominal pains, nausea, and vomiting on April 4, 1950. Her dinner some hours prior to the onset had consisted of a Manhattan cocktail, lamb, asparagus, spinach, and sarsaparilla soda. The next morning (April 5) she discovered many small and large purpuric spots on her face and chest. No other symptoms were noted at this time. Past history obtained revealed an attack of urticaria at the age of eleven, frequent joint pains on many occasions, and the diagnosis of rheumatic fever at the age of 3. Physical examination was negative except for many purpuric lesions on the face, chest, and buttocks, some being as large as a fifty-cent piece. The spots did not blanch on pressure, and the Rumpel-Leede test was negative. The tentative diagnosis of allergic purpura was made, and the patient was given Chlor-Trimeton 4 mg three times daily after meals. She was also referred to our clinic for further investigation. Within seventy-two hours the purpura had almost immediately regressed to the brown color stage. By April 15 there were no traces left of the purpura.

The clinical work-up that followed consisted of intradermal food and inhalant tests and laboratory work-up. The findings (April 24) were as follows: red blood cells 4,600,000, hemoglobin 14.5 gm, white blood cells 6,900, with a differential of 65 polymorphonuclear cells, 31 lymphocytes and 4 eosinophiles. Bleeding time was 1¾ minutes, and clotting time

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RAGWEED POLLINOSIS (HAY FEVER)—A PUBLIC HEALTH PROBLEM IN SCHOOL CHILDREN

Preliminary Report

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THIS preliminary study was undertaken in an attempt to determine whether ragweed pollinosis (hay fever) constitutes a public health problem in school children. It had been noted by one of the authors in his practice in Rochester, New York, that children suffering from hay fever and its complications, particularly bronchial asthma, are, nevertheless, obliged to return to school which, in New York State, customarily opens immediately following Labor Day, the first Monday of September. By an unfortunate coincidence, the peak of the ragweed pollen season is commonly reached at about that time. Besides the fact that children actually suffering from hay fever must return to school, others, whose parents can afford to send them to camps in the mountains and other places of low pollen incidence, must return to the city during the period of maximum pollution of the air with ragweed pollen, and as a result, suffer accordingly. Their ability to study is impaired and some are incapacitated to such an extent as to necessitate absence from school. Since the amount of pollen in the air falls off rapidly after the first week of September, a preliminary study of two high schools and three grade schools was undertaken in order to determine whether a significant percentage of school children would be benefited by delaying the fall opening of school by at least one week.

In co-operation with the Health Bureau of the City of Rochester, the Department of Health Education, and the personnel of the individual schools concerned, a questionnaire was given to each of the pupils to take home for his parents to fill out and return to the school. For obvious reasons, it was felt that this questionnaire should be made as simple as possible. The following three questions were asked:

1. Does the child have any symptoms of hay fever during the first or second week of September?
2. Does the child leave Rochester to get relief? First week in September? Second week in September?
3. Does the child have asthma from ragweed pollen during the first or second week of September?

Each of the above questions was to be answered by "yes" or "no" under separate columns headed "first week" and "second week." The teachers were given the responsibility for seeing that the questionnaires were properly filled out.

From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry and the Health Bureau of the City of Rochester, N. Y.

TABLE I

Schools Surveyed	Number Replying	Ragweed Symptoms		Asthma Due to Ragweed		Children Leaving Rochester for Relief
		No.	Percent	No.	Percent	
Franklin High	326	46	14	12	3	5
Marshall High	448	57	12	24	5	2
No. 11 (Grade)	385	26	6	6	1	4
No. 33 (Grade)	590	21	3	13	2	1
No. 41 (Grade)	391	28	7	12	3	1
	2140	178	8	67	3	13

RESULTS

The results of the survey are tabulated in Table I. A total of 2140 questionnaires were filled out and returned. Of these 178 (8.3 per cent) reported having symptoms from ragweed during the first two weeks of school, sixty-seven (3.1 per cent) reported asthma due to ragweed, and thirteen (0.6 per cent) were obliged to leave or could afford to leave Rochester and school for relief of their symptoms.

As one might expect, the incidence of hay fever between the high school students and grade students differed quite strikingly. Of 774 surveyed high school students, 13.3 per cent had hay fever in contrast to 5.5 per cent of 1,366 grade school students.

DISCUSSION

Generally speaking, the incidence and severity of ragweed pollinosis varies directly in proportion to the amount of ragweed pollen in the air. The summer in which this study was made (1948) the total ragweed precipitation on our slides from August 1 to September 30 inclusive was 1,528 granules per unit (theoretically a cubic yard of air). This was the mildest pollen year in the nine years we have been doing pollen counts. The worst pollen season was 1941, when the total precipitation was 7842. In the past season of 1949, the total precipitation was 5725. Had our studies been made in either of these years, a much higher incidence of pollinosis would certainly have been found in our school children. It is doubtless true that there are many unrecognized mild cases of pollinosis which would not be noted in such a survey. This, however, is not important for this study, since such children can attend school without undue difficulty.

For the purpose of determining the relative contamination of the air by ragweed pollen in various localities, Durham[1] has devised a formula for computing what he terms the "pollen index." This index is derived from a formula involving several factors: the number of days in the season when the pollen concentration reaches 25 granules per cubic yard of air, the maximum daily pollen precipitation, and the total pollen precipitation per cubic yard of air per season. In the course of years since the "pollen index" was first announced, allergists have found that the height of

the index very closely parallels the incidence and degree of morbidity for ragweed pollinosis in any given locality. In Rochester, New York, the average pollen index for eight consecutive years up to 1948 inclusive was 59. Pollen indexes of some other localities are as follows: Albany 36; Boston 17; Buffalo 75; Chicago 75; Denver 31; Detroit 83; New York (Manhattan) 29; Old Forge 0.15; Syracuse 43. A place may be considered as a reasonably good hay fever resort if the pollen index is 5 or less.

The incidence of ragweed pollinosis (hay fever) in the general population has been estimated by various authors to be from 2 to 10 per cent. This study, although the number surveyed is not large, would appear to suggest that about 10 per cent is the incidence of hay fever in the Rochester area. This incidence, as noted above, occurred in a relatively mild pollen season.

It is also generally known that hay fever primarily afflicts young adults, and the majority first develop their symptoms during the second and third decades of life. This is well borne out by the marked difference in incidence in high school students, 13.3 per cent, as compared to the incidence of 5.5 per cent in grade school students. From the public health point of view, this difference is probably significant, as it is the high school student whose education suffers most when he has to be absent from school or has to attend school when he is not feeling well.

Because of the preliminary nature of this survey, many factors which should have been considered were not studied. Although we have roughly determined the incidence of hay fever among the school children of Rochester, we did not study its incidence among the teachers and other school personnel, and we did not determine the severity of the students' symptoms. The last two questions, namely, whether they had asthma and whether they had to leave Rochester for relief, give some indication that at least 3.1 per cent have severe enough symptoms to be benefited by opening schools at a later date. Probably this percentage would be higher, as many parents would undoubtedly like to send their children to areas of low pollen count, but cannot do so for financial reasons.

In this study, no attempt was made to determine whether or not the children with hay fever were receiving proper medical care. Perhaps many of these children could be fairly satisfactorily relieved by hyposensitization together with the use of appropriate drugs.

Whether or not this study is conclusive enough to suggest that public schools should be opened at a later date than is now customary, is a problem for the proper educational authorities to decide. Certainly, an incidence of over 10 per cent in high school students deserves a great deal of consideration, especially when there appears to be no obvious disadvantages to opening school a week or two later than is customary. This would be a more practical measure than air conditioning of the schools to eliminate pollen, because of the prohibitive expense.

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FOLIC ACID AND HISTAMINE

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THIS paper is concerned briefly with the effects of folic acid on the histaminic shock in guinea pigs.

It has been already reported that folic acid is able to inhibit anaphylactic shock in guinea pigs.[7] This inhibition is present also when using vitamine B_{12}, another substance which has proved to be effective in the treatment of macrocytic anemias.[6] In the case of vitamine B_{12} an antihistaminic activity has also been shown to be present.[8] Since it seems that the release of histamine accounts for the anaphylactic shock in animals,[1,2,5] it was natural to see whether the antianaphylactic activity of folic acid might have been due to an antihistaminic activity.

With the following experiments an attempt is made to see whether folic acid is able to inhibit the histaminic shock in guinea pigs.

Fifteen guinea pigs (medium weight 400 gm) were divided into two groups. One group of four, used as control, received intracardiacally 0.4 mg of histamine, which in experiments previously reported has proved to be lethal.[4] After the injection of histamine three of the animals died and one of them, although showing severe signs of shock, survived. The other eleven guinea pigs received 40 mg intraperitoneally and ten minutes later 0.4 mg per kg of histamine. All of them recovered, showing only very slight signs of shock. The same experiments were repeated using larger doses of histamine. Eight guinea pigs (400 gm medium weight) were given 40 mg of folic acid intraperitoneally and ten minutes later 0.8 mg of histamine intracardiacally. Six of them died and only two recovered after having shown severe signs of shock. In five other guinea pigs (400 gm medium weight), even using 60 mg of folic acid for each animal, it was not possible to prevent the death following the injection of 0.8 mg of histamine intracardiacally.

These results indicate that folic acid, when used in large doses, shows an antihistaminic activity which seems to be limited. The fact that folic acid inhibits the anaphylactic shock, while not able to prevent the shock with a dose of histamine greater than 0.4 mg per kg, gives support to the idea already expressed that the histamine released during the anaphylactic shock must be approximately one lethal dose, namely 0.4 mg per kg.[2,3]

ACKNOWLEDGMENT

The folic acid (Folvite) was supplied by the Lederle Laboratories through the courtesy of Dr. J. M. Ruegsegger.

(References on Page 270)

Present address of Dr. Traina: Sacred Heart Hospital, Pensacola, Florida.

Convention Echoes

ODYSSEY OF AN ALLERGIST
The Presidential Address

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Columbus, Ohio

As your retiring President, I am given the opportunity to address you on a subject of my own choosing in the field of allergy. In considering what might be appropriate, the problem cases were uppermost in my mind. Few will deny that confusion in diagnosis with failure in treatment is a common experience for all of us. Why then, with the modern procedures for measuring deviations in bodily function, do we continue to encounter so many difficulties?

My feeling is that with the advent of the newer diagnostic methods, there has been a growing tendency to lose contact with the total person, in our preoccupation with the assessment of his parts. More and more emphasis is focused on efforts by the physician to interpret disorders in the light of physical data. What the patient says and does becomes less and less significant. How he feels and thinks is considered unimportant.

The concept that there are powerful forces for integration and growth within each person has been replaced by the assumption that drugs, diets and directions are the major requisites in the treatment of most diseases. The sick person is becoming a patient in the original sense of the word. Passivity and dependency upon the decisions and manipulations of the physician are tending to exclude him from active participation in his own recovery. Since data concerning the patient's knowledge of himself is unmeasurable by the usual clinical and laboratory methods, its use in the evaluation of his state of health is considered unscientific.

This change is readily understandable when we recall the great advances in the physical and biological sciences during the past eighty years. From Pasteur to penicillin is a glorious era in medical history. Methods for the detection, prevention and cure of infectious diseases and deficiency states, as well as for direct attacks upon localized disease processes, have been so fruitful that we have come to look upon them as a possible solution for all the ills of mankind. Medical education and hospital administration are geared to the implementation of these principles in the training of physicians and in the care of the sick. The theory and practice of medicine as a whole reflects these attitudes, and the specialty of clinical allergy has not escaped their influence.

For forty years now, we have been in what might be called the immunologic era of allergy, which followed the demonstration by Noone and Freeman in 1911 that hay fever could be successfully prevented by preseasonal inoculations of gradually increasing amounts of an aqueous extract of grass pollen. This discovery, that the principles of immunology could be applied to hay fever, opened a vast new field for exploration. Since avoidance of offending allergens was not always practical, here was an alternate method of treatment. Specific immunity to a specific non-bacterial agent was now possible.

The immediate wheal reaction following the application of grass pollen to a

Presented as the Presidential address, Seventh Annual Congress of the American College of Allergists, Edgewater Beach Hotel, Chicago, Illinois, February 11-14, 1951.

superficial skin scratch had been known since the publication of Blackley's monumental experiments in 1873. The use of the patch test in identifying allergens producing dermatitis on direct contact with the unbroken skin was introduced by Jadassohn in 1895. These simple procedures, plus the diagnostic information obtained from the history and from clinical trial with suspected allergens, provided a new approach to many medical problems. Their application to such varying disorders as seasonal and nonseasonal asthma and rhinitis, acute urticaria and contact dermatitis, was rewarded with brilliant success in many instances.

With increasing experience and the many favorable reports of successful diagnosis and therapy, what might be regarded as a philosophy of allergy was formulated. The conviction grew that in all these disorders a specific extrinsic allergen comes in contact with specifically sensitized cells, liberating a histamine-like substance which, in turn, produces dilatation of the minute vessels, contraction of involuntary muscles and hypersecretion of mucous glands. Therefore, one must search diligently for the allergen, and once identified, it is to be avoided. Tolerance can usually be established by increasing inoculations of the allergen, if avoidance is not possible. In spite of the many successes where there was conformity with the basic hypothesis, there were also many failures.

Failures in diagnosis were attributed to crudely prepared testing extracts, to the use of an insufficient number of skin tests, to the scratch method of testing, to obscure or unknown allergens, or to a refractory state of the skin. With the hope that further refinements would overcome these difficulties, testing extracts were prepared by special chemical methods; diagnostic tests were multiplied; the intracutaneous method of testing was introduced; and various forms of dietary manipulation were recommended.

Failures in therapy were attributed to inadequate or excessive dosage or to the inability or unwillingness of the patient to follow instructions as to avoidance of the allergen. Accumulating experience, however, seemed to indicate that in spite of refinements in the immunologic approach many cases failed to conform to the pattern of allergy.

When a specific extrinsic cause could not be identified, the hypothesis of bacterial allergy was invoked. Reasoning from the analogy of the tuberculin test, it was assumed that the delayed twenty-four-hour erythema, following the intracutaneous injection of pure cultures of various microörganisms, indicated specific hypersensitiveness to the protein of the bacterium as well as a causal relationship with the clinical symptoms.

Some success followed the use of autogenous vaccines in treatment, but an equal number of patients were improved by the use of stock vaccines or vaccines prepared from organisms totally unrelated to the disorder such as colon bacillus, whooping cough vaccine, and typhoid vaccine. Later it was discovered that a number of nonbacterial substances such as 1 per cent sulphur in Wesson oil, spleen extract, wide field x-ray therapy over the body, deep x-ray therapy directed to the hila of the lungs, peptone, and histamine were all followed by some measure of success. But, again, results were inconsistent, and it was concluded that whatever the mechanism, it was probably nonspecific.

Although ACTH and cortisone are capable of inducing remissions, their unfavorable physiologic effects preclude continued use. Valuable as these hormones are in research and in the management of the desperately ill asthmatic patient, their use in chronic cases is limited. They appear to be most helpful where acute symptoms of short duration are anticipated. If this assumption proves valid, an effective form of nonspecific therapy for the control of seasonal asthma and hay fever, acute drug allergy, and contact dermatitis will be available.

As the search for a better understanding of the problem case continued, the term

"intrinsic" appeared in our vocabulary to differentiate the group in which extrinsic allergen could be identified. It did not imply an essentially different mechanism but was an admission that extrinsic factors were not always necessarily involved. However meager this change in our philosophy, attention was focused upon possible factors within the patient himself. Basic principles, as originally conceived, were now questioned.

Clinical similarities between intrinsic and extrinsic cases were so striking it is understandable that persistent efforts to identify a specific physical or chemical factor continued. Granting that there are close clinical similarities between the two groups, let us examine the more obvious differences.

Patients with extrinsic allergy, seasonal or nonseasonal, give a concise, reasonable history so that the experienced physician can strongly suspect and often be reasonably certain of, the causative factor. If it is of plant or animal origin, positive immediate wheal reactions to scratch tests can be expected. If it is a contact allergen, patch tests will be diagnostic. Indisputable proof of the cause-and-effect relationship rests finally upon the consistent reproduction of symptoms with the disguised allergen. Avoidance of the offending allergen brings relief within a few hours or a few days. If necessary, satisfactory immunization can be induced. Seasonal hay fever and asthma, acute urticaria, drug allergy, and contact dermatitis fit into this pattern, as do a few perennial cases. Characteristically, the symptoms are acute.

However, in most nonseasonal syndromes such as perennial vasomotor rhinitis, perennial intrinsic asthma, chronic urticaria, atopic dermatitis, and chronic gastrointestinal disorders, the patient gives an illogical and unreasonable history blaming all sorts of extrinsic factors which cannot be correlated with the symptoms. In addition, there are many collateral complaints such as fatigue, nervousness, headaches, sleeplessness, heart consciousness, and various aches and pains which add to the confusion. Skin tests are usually negative or, when positive, are nonconfirmatory. Clinical trial with disguised allergens is equivocal and often confusing, and typical symptoms cannot be reproduced with any degree of consistency. Fixed organic change or infection, sufficient to account for the syndrome, cannot be demonstrated. Clinically, the most significant characteristic is chronicity. The frustrating experience of managing these cases with the various forms of symptomatic and nonspecific therapy available is well known.

Although these two groups are sharply separated for purposes of discussion, mixed extrinsic and intrinsic cases are frequently encountered. An evaluation of the significance of each component is not always easy.

It seems clear, then, from the history of allergy during our generation, that the theory of specific hypersensitiveness has failed to explain many chronic cases. Instead of accepting this as fact, further efforts are being made to squeeze varied disorders into the pattern of allergy. The result is that the allergic hypothesis is sometimes stretched to the breaking point to accommodate a troublesome syndrome. Minor variations in intracutaneous tests are interpreted as positive; fluctuations in peripheral leukocytes following the ingestion of suspected foods are thought to have diagnostic significance; clinical trial with undisguised foods is considered unequivocally positive when there is an increase in a constellation of such minor objective and subjective phenomena as pulse rate, fatigue, coughing, sneezing, stiffness in the neck, and generalized muscular aching. Some investigators are unable to entertain the possibility that perhaps a different approach might be fruitful. Others, because of failure, discouragement, and frustration, are ready to re-assess the problem in the light of other hypotheses—and, I might add, almost any other hypothesis. Many believe that the key of immunology cannot unlock the problem case and the lock cannot be forced; the correct key must be found and tried.

A slow, almost imperceptible transition in my own thinking began with a visit to

Long Island in 1938. George Bray, facing similar difficulties, was using an inhalant mixture of house dust, horse dander, orris root, and feathers (Bencard's mixture), in his problem cases of asthma and rhinitis. John Freeman, on the other hand, treated with autogenous vaccines prepared from pharyngeal cultures, when prick tests to common inhalants and foods were negative. Although he made no clear-cut statement, he left the impression that psychologic influences were sometimes significant.

But it was Livingston who first opened the door and let in a little light for me. Some of you will recall his photographically illustrated booklet describing breathing exercises for asthma. Here is the story he told me:

> "After the war, a woman gymnast, a physical culture teacher, came from Germany to London claiming she could help asthma with breathing exercises. She asked me to refer her only my worst cases; those who had failed to respond to the usual methods of treatment. To my surprise, a number improved remarkably. You should know too, that she was a very dynamic and positive person. But, these attitudes got her into difficulty in her relations with others, and as a result she left us. The work was continued by her assistant, an English girl of an entirely different temperament; not nearly so aggressive. She had little success and yet she used the same exercises and worked with the same group of patients. It then became obvious that the German teacher was achieving results by suggestion rather than by anything of intrinsic value in the breathing exercises themselves."

Here, it seems, is a clear example of misinterpretation of readily observable data, an error physicians must constantly guard against in the evaluation of therapeutic procedures.

Further evidence of the importance of psychologic factors was demonstrated in a series of well-planned and well-controlled experiments comparing the effectiveness of Bencard's inhalant mixture with injections of normal saline in the treatment of perennial vasomotor rhinitis. The Asthma Research Council in its "Report of Progress" for 1938 states:

> "The results of treatment with saline solution were slightly better than those obtained by protein desensitization—from the recent results it appears clear that the psychological element was of even greater importance than he had anticipated."

Eyerman, in 1938, called attention to the significance of emotional factors in asthma and warned against too great a bias by psychiatrists and allergists alike when he said:

> "It seems that those interested in allergy pay too little attention to the psyche and those interested in the psychic conditioning of bronchial asthma are not aware of the possible allergic explanations for the vagaries of this disease."

Voices have been raised from time to time, calling attention to the importance of the emotional component in allergic disorders, but only in recent years have they been heard above the roar of the rushing torrent of immunology.

This, then, is an outline of our heritage, of our cultural conditioning in allergy during the past forty years. I have tried to explain the present in terms of our past philosophy with the hope that changes in thinking will be translated into action, that modifications in theory may be followed by modifications in practice. The evidence seems to suggest that in many problem cases the bodily manifestations are somatic components of emotional disorders and may, therefore, be amenable to the psychosomatic approach. This does not mean that established allergic procedures are to be discarded, but rather that psychological as well as physiological techniques can be used with advantage both in diagnosis and in treatment. Although progress in psychology has paralleled progress in the physical sciences, the barrier of

terminology has separated the two disciplines. Simplification of the language of both will do much to unify them into a useful and realistic approach to the nature of man and to his disorders.

We speak of psychologic and physiologic components of man only because they are observable and measurable by differing techniques. Actually these are two aspects of one inseparable and individual personality. Dissociation comes because we talk in terms of the data obtained by the different methods. But method does not separate man; separation occurs in our own thinking. Only by a proper integration of the information obtained by the varying techniques and its accurate interpretation in the light of man's unity, can we hope to gain a clearer understanding of the disorders which we now classify as emotional or psychoneurotic or psychosomatic.

The problem facing us is a formidable one. Significant psychological components have been demonstrated in at least two thirds of perennial cases which, unless clearly recognized and properly handled, may make all efforts at therapy fruitless. With the growing interest in emotional factors, a need has arisen for further information as to why these disorders develop and how they can be dealt with. But since precise techniques can best be demonstrated by electrical recordings or verbatim type-scripts of the actual interviews, they will not be described here. However, a few guiding principles may prove helpful.

1. Each personality, in working out life's problems, needs opportunity for satisfying achievements in an atmosphere of love and understanding.

2. Most conflicts arise in attempts to adapt to life situations relating to self, to others, or to the more ultimate problems of the meaning of life and death and one's orientation in the universe.

3. Feelings of being rejected by those from whom we expect love, generate fear, anger, guilt, bodily disorders, and changes in behavior which are defensive reactions to psychological pain and stress—phenomena which are, all too often, misinterpreted by doctor and patient alike.

4. Normal emotional reactions are transient and reasonable; the cause and effect are clearly recognized.

5. Emotional disorders are amplified and prolonged emotional reactions without an understanding of the relationship between cause and effect.

6. The more disordered the emotions, the greater the defensiveness to an intellectual explanation of the illness.

7. Vasomotor changes, localized edema, contraction of involuntary muscle, and increased secretion of mucous glands are components of emotional as well as allergic disorders.

8. Successful psychotherapy depends more upon the willingness of the patient to face his problems and then ultimately himself, than upon his intellectual capacity.

9. Skill and experience in interviewing are important, but much depends upon the attitude of the physician in developing a good inter-personal relationship.

10. The physician having the proper attitudes to establish a healthy relationship with his patient is usually the best one to continue psychotherapy.

11. An adequate physical examination and suitable laboratory tests are reassuring to patient and doctor alike.

12. Man does not live by bread alone; the allergist must bring acceptance and understanding as well as adrenaline and ragweed pollen, into the doctor-patient relationship.

13. In psychotherapy, the accurate relating of cause and effect is called insight. Since disordered emotional reactions are habitual patterns, physiologically mediated, insight alone may be insufficient; only by persistent trials will the old tendencies be overcome. Insight, being an intellectual activity, is not necessarily followed by

readjustment of bodily function. "The Lord will forgive our sins, but the nervous system never does."

Once the emotional nature of a disorder is recognized, the problem of psychotherapy presents itself. In searching for a suitable method, the client-centered, feeling-reflecting counseling technique described by Carl R. Rogers proved readily adaptable to medical history-taking and to further interviews with emotionally disturbed patients. During the original interview the physician maintains an attentive and an accepting attitude, permitting the patient to tell his story in his own way, without interrupting or questioning. In addition to being a good listener he tries to sense the feelings rather than the intellectual content of what the patient says and during pauses calmly and concisely reflects these back to him. Intercommunication of understanding releases dynamic forces which permit a free expression of feelings about difficulties in inter-personal relationships and conflicts in personal matters. In the successful case the patient begins to realize that his bodily disorders are related in some way to his feelings. At subsequent visits he may report improvement in his symptoms and the original negative attitudes change to positive ones. As insight is gained he begins to weigh and finally to choose courses of action which he hopes will bring about a solution. Finally, by persistent effort in the life situations which he experiences between interviews, he arrives at what is to him, a satisfactory state and terminates the relationship. But psychological growth, once begun, continues and the knowledge gained is useful in coping with future difficulties. Since life is a continuous series of decisions, it is understandable that after months or years new and greater problems may arise which require further counseling.

Considerable difficulty arises from an inability or unwillingness to accept the possibility that repressed feelings and conflicts can cause bodily disorders. This is not only a new concept but it implies some measure of personal responsibility for the illness and for working out the solution. Since there is, in all of us, the capacity for making free choices, it is understandable that many patients do not follow this typical pattern. A few persist in focusing attention on bodily sensations and require prolonged symptomatic treatment. Others progress to the point of insight but are unable to make the necessary decisions to change. When there is a persisting tendency to blame a father, a mother, an authoritative person, or a frustrating situation, the therapeutic process stalls. Rejecting attitudes of parents are significant factors in the formation of emotional disorders, but lasting success in therapy is seldom achieved until the patient is able to assume responsibility for his own manner of reacting and to take appropriate means to change. However, a sufficient number work through to a satisfactory conclusion to make this approach valid and worth while. Many who were failures with conventional allergic management have been aided to the re-establishment of normal health and happiness. Rather than attempting to enforce rigid conformity to the rules of technical procedure, the wise physician will adapt his approach to the attitudes and feelings of each patient.

With the integration of these concepts into the philosophy of allergy, a broad and fruitful area will be open for the discovery of new "allergens" to which the "sensitized" personality reacts. Warmth, understanding and patience are the cardinal virtues required to create a suitable "climate" for the patient to "immunize" himself to disturbing life situations, past and present.

And now that I am about to be "promoted" to the office of Past President, May I introduce you to the philosophy of my able and enthusiastic successor, Harold A. Abramson, who summarized much of this presentation in a single paragraph when he said:

"If we include the basic science of psychodynamics as part of the discipline of the allergist, the practice of allergy will be released from the restriction imposed by the

specificity of immunologic reaction. The field of the allergist defined in this broader sense, need not then depend upon variations in immunologic specificity alone, but is expanded to include altered reactivity by other processes. It is the application of psychodynamics to these processes which is now required for understanding and treating those clinical entities."

695 Bryden Road
Columbus 5, Ohio

THE AMERICAN COLLEGE OF ALLERGISTS

Proceedings of Seventh Annual Congress

The Seventh Annual Congress of The American College of Allergists was held at the Edgewater Beach Hotel, Chicago, Illinois, February 11-14, 1951. It was combined with and preceded by (February 9-11) a three-day intensive Graduate Instructional Course in Allergy. The number of physicians registering for the Congress and for the Instructional Course combined totaled 435. Thirty-nine technical exhibitors were present and exhibited products relating to allergy, and there were ten scientific exhibits. The Program Committee, of which Dr. Albert V. Stoesser was chairman, are to be congratulated on the successful instructional course. There were a number of cancellations on account of weather conditions, but 129 attended the course. The officers of the College are most grateful to the instructors who contributed toward making this course a success.

Dr. Norman W. Clein, on Sunday evening following the instructional course, presented a most interesting illustrated lecture on "The Atom Bomb—What It Does!—What You Can Do!"

The Scientific Session opened Monday morning with a general session. Monday afternoon there were six papers on psychosomatic allergy. A delightful cocktail party, sponsored by the Schering Corporation of Bloomfield, New Jersey, was given in the West Lounge on Monday evening, following which Dr. Herman Heise showed entertaining colored movies.

On Tuesday morning, Dr. John H. Mitchell gave his presidential address, followed by the guest speaker, Dr. Arild E. Hansen, Chairman, Department of Pediatrics, School of Medicine, University of Texas, Galveston, Texas. His subject was "Dietary Fat in Relation to the Integrity of the Skin." At 10:15 the open business meeting was held.

Business Meeting

The following officers were elected and, in due course, have assumed their respective offices and will serve until their successors are duly elected and qualify:

President—Harold A. Abramson, M.D.
President-Elect—J. Warrick Thomas, M.D.
First Vice President—G. Estrada de la Riva, M.D.
Second Vice President— L. Dell Henry, M.D.
Secretary-Treasurer—Fred W. Wittich, M.D.
Assistant Secretary-Treasurer—Albert V. Stoesser, M.D.

Board of Regents:

3-Year Term	*2-Year Term*	*1-Year Term*
Hyman Miller, M.D.	Norman W. Clein, M.D.	John Gillaspie, M.D.
Bret Ratner, M.D.	L. O. Dutton, M.D.	Hugh Kuhn, M.D.
Walker Rucks, M.D.	Stephan Epstein, M.D.	Herbert Rinkel, M.D.

Dr. Harold A. Abramson, as President, becomes the tenth member of the Board of Regents.

Dr. Wittich, Secretary-Treasurer, presented a complete financial report covering the ANNALS OF ALLERGY for the year ended November 30, 1950.

Dr. George E. Rockwell, chairman of the Finance Committee, presented a written report covering College finances for the calendar year 1950, and this was supplemented by a complete certified audit report of the College.

The chairmen of the various committees, Dr. Morris Scherago, for the Advisory Council on Standardization; Dr. James Stroh, for the Pollen Committee; Dr. George E. Rockwell, for the Rheumatism and Arthritis Committee; Dr. E. A. Brown, for the New and Unused Therapeutics Committee; Dr. Harold Abramson, for the Subcommittee on Publications and Subcommittee for Standardization of Aerosol Therapy; Dr. Jonathan Forman, for the Extension of Postgraduate Education Committee, all delivered reports on behalf of their respective committees which were accepted and approved.

An Honorary Fellowship was conferred upon Professor Clyde Christensen, Professor of Plant Pathology, of the University of Minnesota School of Agriculture.

Dr. William Kaufman of Bridgeport, Connecticut, was appointed chairman of the Publicity Committee, and he will have charge of all publicity relating to College matters.

The Secretary-Treasurer reported that the membership is now in excess of 1,000.

We report with sorrow that during the past year the College sustained through death the loss of the following members:

Dr. William F. Petersen
Dr. Paul Staman
Dr. Herbert N. Vermilye
Dr. John DeCarlo

Obituaries appeared in the ANNALS OF ALLERGY, and condolences were sent to the families.

The Nominating Committee, consisting of Drs. L. O. Dutton, chairman; George E. Rockwell, Hal M. Davison, Hyman Miller, Norman W. Clein, and Stephan Epstein, after due deliberation and consideration, submitted the following slate on the official ballot to be voted on at the 1952 annual election as follows:

President-Elect—Murray Peshkin, M.D.
First Vice President—Morris Kaplan, M.D.
Second Vice President—Henry D. Ogden, M.D.
Secretary-Treasurer—Fred W. Wittich, M.D.
Assistant Secretary-Treasurer—Albert V. Stoesser, M.D.

Board of Regents—3-Year Term
Harry S. Bernton, M.D.
Vincent Derbes, M.D.
L. E. Seyler, M.D.

Mr. Eloi Bauers, counsel for the College, who was in attendance at all business sessions held in Chicago, presented in booklet form a printed set of By-Laws for the regulation of the affairs of the College. He stated that certain amendments and changes heretofore adopted, and which did not appear in an earlier printing, had now been incorporated in the booklet, and that with the help and assistance of individual Board members, and especially with the help and assistance of Dr. Ethan Allan Brown, many of the separate By-Law provisions as they now appear had been reframed and rewritten. They were thereupon read, article by article, and after full and careful consideration and discussion were unanimously adopted as and for the ByLaws of this corporation, and it was ordered that a printed copy thereof be filed with the minutes of the meeting and copies supplied to all members of the College requesting them.

A dinner-luncheon, sponsored by the College, was held in the Marine Dining Room on Tuesday noon. The spirit and enthusiasm manifested by all who attended was very gratifying. Tuesday afternoon was devoted to a Section on Pediatrics, of which Dr. Bret Ratner of New York City was chairman. There were nine papers presented on this subject. On Tuesday evening the Committee on Dermatologic Allergy conducted a Dermatology Round Table, for which Dr. Rudolf L. Baer acted as Moderator. The participants were Drs. Herbert Rattner, Stephen Rothman, James R. Webster, Morris Leider, Adolph B. Loveman, Stephan Epstein, and Adolph Rostenberg.

Wednesday morning opened with the Section on Otolaryngology, of which Dr. George Shambaugh was chairman. This symposium was composed of three papers. The Section on Dermatology occupied the second half of the morning, for which Dr. Morris Leider was chairman. Four papers were presented. On Wednesday afternoon there was an outstanding Panel on Rheumatism and Arthritis, at which Dr. George E. Rockwell presided. Six papers were presented at this Panel.

Next Annual Congress

The next Annual Congress of the College will be held at the Hotel William Penn in Pittsburgh, Pennsylvania, April 4-9, 1952. An excellent local committee headed by Dr. James Mansmann of Pittsburgh, has already done a great deal of preliminary work to assure the success of this meeting. The meeting will be combined with and preceded by an excellent Instructional Course featuring sessions on Industrial Allergy which, we are already assured, will attract widespread attention to the convention. The Instructional Course will be under the supervision of Dr. Hal Davison of Atlanta, Georgia.

In 1953, the College will again hold its annual meeting in Chicago, with Dr. Morris Kaplan as chairman of the local committee on arrangements.

At the present time, it is planned that the 1954 meeting will be held in San Antonio, Texas, with Dr. Boen Swinny as chairman of the local committee on arrangements.

Dr. Giles A. Koelsche, Consultant Physician, Division of Internal Medicine, Mayo Clinic, Rochester, Minnesota, has accepted the chairmanship of the Program Committee for the Pittsburgh meeting, and is already at work with Dr. Harold Abramson, President, and Dr. Fred Wittich, Secretary-Treasurer, the other members of the committee.

Registration will begin on Sunday, April 6, 1952, at 2:00 p.m., and will not, in any way, interfere with attendance at the Instructional Course. Following the custom already established, there will be no technical or scientific exhibits on Sunday. These will be featured on Monday, Tuesday and Wednesday, April 7, 8 and 9. A scientific program will also be held on these three days. As formerly, there will be sections on Psychosomatic Allergy, Pediatrics, Dermatologic Allergy, Otolaryngology, as well as one on Rheumatism and Arthritis.

Report of the Committee on New and Unused Therapeutics for 1951

The Committee on New and Unused Therapeutics is composed of L. O. Dutton, M.D.; John D. Gillaspie, M.D.; L. Dell Henry, M.D.; Stanislaus H. Jaros, M.D.; Cecil M. Kohn, M.D.; Morris Leider, M.D.; E. J. Luippold, M.D.; Bret Ratner, M.D.; Perry Sperber, M.D.; and Ethan Allan Brown, M.D., chairman.

In the time which intervened since the last report, various members of the committee studied a number of drugs, the results with which were so disappointing that it was not felt worthwhile to make separate detailed published reports. Completely negative results followed the use of oral procaine in nineteeen of twenty patients, the group containing representative cases of bronchial asthma and atopic

eczema. Para-amino-benzoic acid sodium was used in 2 gm doses in six patients with atopic eczema, with no results in any.

Adenosine-5-Monophosphate (My-B-Den) was used in the treatment of contact dermatitis and atopic eczema in accordance with the schedules in the literature, namely, 1 cc at intervals of one hour for five doses for two or three successive days. In none of fifteen patients was there any amelioration of the pruritus or of the condition itself.

A material of unknown composition known as "Zuccala antigen" was used in over 100 patients with bronchial asthma, with no results which could be ascribed to causes other than natural remissions or to the incidental treatment given.

Extracts of Khellin, in various forms, were used in approximately twenty patients, with side reactions of nausea and vomiting, as well as gastric distress, occurring in the majority, the symptomatic relief not being any different or greater than that using other agents.

The use of ACTH and cortisone in allergic conditions was being reported upon so widely by both members of the College and of the committee that it was not considered necessary for the committee to make this one of its pilot tests during the past year. The members of the committee, however, in conference, felt that their experience with these drugs and their knowledge of the literature required a definite stand. The following resolution was passed and presented to The American College of Allergists at large as a motion which was passed at the annual meeting of the college at the Edgewater Beach Hotel, February 9-11, 1951.

Resolution

In view of the widespread lay publicity and the apparently unrestrained medical use of adrenocorticotropic hormone and cortisone, the Committee on New and Unused Therapeutics of The American College of Allergists feels that its attitude toward these drugs should be presented to The American College of Allergists and, if possible, to the public at large.

It is now known that both ACTH and cortisone modify many of the superficial clinical manifestations of hypersensitivity. It is equally evident that excepting in extreme states and in self-limiting conditions, these drugs confer no positive benefit to the patient, suppressing the immune response and having no effect on or actually adversely affecting defensive reactions.

The fact that a number of patients have been permitted to use these drugs for continued self-administration without supervision is to be deplored.

In all cases when the original precipitating factors are not eliminated or controlled, cessation of corticoid therapy is followed by a prompt relapse and recurrence of the original signs and symptoms. They therefore do not replace studies, elimination, injection treatment, psychotherapy and other accepted means of treating allergic patients. The undesirable side effects may be serious and, occasionally, permanent. Let it be resolved that this information be published in an early issue of ANNALS OF ALLERGY and communicated to the medical profession and the public as a stand taken on this subject by The American College of Allergists.

ETHAN ALLAN BROWN, M.D., *Chairman*

Report of the Standardization Committee for 1951

The Standardization Committee of The American College of Allergists met at 3:00 p.m., on February 10, 1951, at the Edgewater Beach Hotel, Chicago, Illinois.

Members present were Drs. M. H. Mothersill, Morris Kaplan, H. E. Prince, J. Warrick Thomas, L. J. Halpin, H. B. Tillman, Roger P. Wodehouse, Harold Abramson, and Morris Scherago, chairman. Dr. Wittich was unable to be present because of conflict with another engagement for the College. The chairman reported that Dr. Maietta had written that he would be unable to attend the meeting.

The first item on the agenda was the report of the Subcommittee on the Certification of Allergenic Extracts. The chairman of this subcommittee (Dr. Scherago) stated that he had written to Dr. Wodehouse and requested him to present his paper on "Standardization of Ragweed Pollen Extracts by Precipitin Reaction" before the Committee on Standardization. He stated further that this paper, together with one to be presented by himself before the Standardization Committee on work done at the University of Kentucky on "Standardization of Dust Extracts. III. Precipitin and Collodion Particle Agglutination Experiments. IV. Rabbit Skin Sensitivity Experiments," would constitute the report of this subcommittee. Dr. Wodehouse then read his paper. The committee discussed the paper, commended Dr. Wodehouse for his work and expressed the feeling that his studies were in keeping with the objectives of the committee. His paper was accepted as a progress report on the effort to standardize pollen extract. Dr. Scherago then presented his paper and it, too, was discussed by the committee. The Committee on Standardization voted to recommend that since, at present, the methods for standardization of extracts are inadequate, studies in this direction should be continued by members of the Subcommittee on Certification of Allergenic Extracts. The second item on the agenda was the report of the Subcommittee on the Standardization of Aerosols by Dr. Harold Abramson, chairman. Dr. Abramson stated that three studies had been carried out by the Subcommittee as follows: (1) Surface Anesthesia of the Respiratory Mucosa by Nebulization, by Joseph B. Miller and Harold A. Abramson; (2) Aerosol Streptomycin Treatment of Advanced Pulmonary Tuberculosis in Children, by Joseph B. Miller, Harold A. Abramson and Bret Ratner; (3) Aerosols III. An Inspiration-Time Meter for Quantitative Measurement of the Inhalation Period of Mists, by H. A. Abramson, H. H. Gettner, and B. Sklarofsky. Abstracts of the three papers were presented by Dr. Abramson, following which there was a full discussion of the three subjects.

The third item on the agenda was a report by Dr. Morris Kaplan on the establishment of a liaison between The American College of Allergists and the laboratories of the American Medical Association, recently established for the study of the composition of foods, drugs, and cosmetics. Dr. Kaplan reported that the American Medical Association Laboratories would be glad to pass on to this committee any reports as to ingredients in foods, drugs, cosmetics, et cetera, and to co-operate to the extent of their ability. The committee recommended the continuation of our liaison delegate.

The fourth item on the agenda was the report on the Handbook of Terminology in Allergy. In the absence of Dr. Maietta, the chairman stated that the manuscript could be completed for publication if those sections still lacking were submitted at an early date. The members of the committee assigned these two sections (Drs. Kaplan and Prince) agreed to submit them within thirty days. The committee then voted to recommend that the services of a professional editor be obtained to assist in editing the Handbook, after all the members of the committee had reviewed the completed work and the final manuscript had been submitted to a severe critic. The committee voted to request the Board of Regents to provide a budget of $100.00 for the expense of editing. The committee voted to make an informal report at a later date to the Board of Regents concerning possible publication costs, selling price, et cetera. The committee meeting adjourned at 4:35 p.m.

The above report was presented at the meeting of the Board of Regents on February 10. After considerable discussion, the Board of Regents voted to accept the report and to appropriate $100.00 for the professional editing of the Handbook. The Board of Regents also voted to direct the committee to refer the finished manuscript to the chairmen of the various specialty committees of the College for their review and criticism.

TECHNICAL EXHIBITORS, EDGEWATER BEACH HOTEL

February 11-14, 1951

ALLERGEN-PROOF ENCASINGS, INC., Cleveland, Ohio. Allergen-proof encasings for avoidance of house dust and other allergens.
ALLERGY-FREE PRODUCTS, Brooklyn, New York. Bedding, beds, pillows, electrical equipment, cosmetics, and air conditioning for the allergen-free home.
ALMAY—Division of Schieffelin & Co., New York, New York. Elegant hypo-allergenic cosmetics.
AMERICANA CORPORATION, Chicago, Illinois. *Encyclopedia Americana* and *Book of Knowledge.*
THE ARMOUR LABORATORIES, Armour and Company, Chicago, Illinois. Acthar (ACTH).

BAXTER LABORATORIES, INC., Morton Grove, Illinois. Pyromen for allergic disorders.
BILHUBER-KNOLL CORP., Orange, New Jersey. Quadrinal, an anti-asthmatic and Valoctin, a new sedospasmolytic.
THE BORDEN COMPANY, New York, New York. Mull-Soy, the hypo-allergenic soy food.
BRUCE PUBLISHING COMPANY, St. Paul, Minnesota. *Annals of Allergy* and *Quarterly Review of Allergy and Applied Immunology.*
BURROUGHS WELLCOME & CO. (U.S.A.), INC., Tuckahoe, New York. Perazil, a new antihistamine.

THE CHICAGO DIETETIC SUPPLY HOUSE, INC., Chicago, Illinois. Special flours, rice, soybean and barley wafers, canned rye bread.
CHILCOTT LABORATORIES, DIVISION OF THE MALTINE COMPANY, Morris Plains, New Jersey. Cellothyl for control of gastrointestinal disorders and Tedral for bronchial asthma.
CIBA PHARMACEUTICAL PRODUCTS, INC., Summit, New Jersey. Pyribenzamine hydrochloride and Antistine.
THE COCA-COLA COMPANY. Ice-cold Coca-Cola.

THE DeVILBISS COMPANY, Toledo, Ohio. Atomizers, nebulizers, and vaporizers.
DOHO CHEMICAL CORPORATION, New York, New York. Auralgan, O-tos-mo-san, Rectalgan, and Rhinalgan.

EISELE AND COMPANY, Nashville, Tennesseee. Precision syringes and hypodermic needles.
ENCYCLOPAEDIA BRITANNICA, Chicago, Illinois. *Encyclopaedia Britannica.*

E. FOUGERA AND CO., New York, New York. Aveeno for skin irritations.

GRAHAM LABORATORIES, Dallas, Texas. Oleoresin extracts for diagnosis and treatment of contact dermatitis due to plants; syringes, needles, serum vials.
GRUNE & STRATTON, INC., New York, New York. Quality medical books.

HOLLISTER-STIER LABORATORIES, INC., Spokane, Washington. Items for use in diagnosis and treatment of allergic disorders.

INTERNATIONAL ASSOCIATION OF ALLERGISTS, Minneapolis, Minnesota. Featuring forthcoming First International Congress on Allergy in Zurich, Switzerland, September 23-29, 1951.

LEWYT CORPORATION, Brooklyn, New York. Lewyt vacuum cleaner.
ELI LILLY AND COMPANY, Indianapolis, Indiana. Aerolin Compound for asthma, Hista-Clopane for allergic rhinitis.

LUZIER'S, INC., Kansas City, Missouri. Fine cosmetics and perfumes.

MARCELLE HYPO-ALLERGENIC COSMETICS, INC., Chicago, Illinois. The original "hypo-allergenic" cosmetics.

MERCK & CO., INC., Rahway, New Jersey. Neo-Antergan for symptomatic relief of allergic diseases.
THE WM. S. MERRELL COMPANY, Cincinnati, Ohio. Decapryn, the long-lasting antihistamine.

PARKE, DAVIS & CO., Detroit, Michigan. Pharmaceutic, antibiotic and biologic lines.
PHILIP MORRIS & CO. LTD., INC., New York, New York. Fine cigarettes.

REXAIR DIVISION, MARTIN-PARRY CORPORATION, Toledo, Ohio. The vacuum cleaner that traps dust in water.

SANDOZ CHEMICAL WORKS, INC., PHARMACEUTICAL DIVISION, New York, New York. Gynergen, Digilanid, Scillaren, Scillaren B, Calglucon and Sandoptal.
SCHERING CORPORATION, Bloomfield, New Jersey. The Chlor-Trimeton Maleate and Trimeton.
SHARP & SHARP, Everett, Washington. Pollens and powdered allergens.
STEMEN LABORATORIES, INC., Oklahoma City, Oklahoma. Manufacturers and collectors of more than 600 allergens.

TEXAS PHARMACAL COMPANY, San Antonio, Texas. Pharmaceuticals and Allercreme hypo-allergenic cosmetics.

WINTHROP-STEARNS, INC., New York, New York. pHisoderm with Hexachlorophene, Isuprel, Neo-Synephrine with Thenfadil.
WYETH, INCORPORATED, Philadelphia, Pennsylvania. Neohetramine and Allergens in Tubex.

ALLERGIC PURPURA RESPONDING TO ANTIHISTAMINIC THERAPY

(Continued from Page 225)

4 minutes. Platelets were 360,000. Kahn test was negative. Urinalysis was normal except for 1-plus albumin.

Intradermal Positive Reaction

Feathers +	Asparagus ++	Prune +
Plaintain +	Lettuce +	Cantaloupe +
Wheat +	Cabbage +	Apricot +
Milk +	Strawberry +	

During the period between April 21 and July 7 there has been no recurrence of the purpura, though the patient had been instructed to indulge heavily in the foods that had been found to be positive.

We have presented the case of a young woman with a past history of allergy and with acute onset of abdominal pains, nausea, vomiting, and purpura. The work-up definitely ruled out the nonallergic purpuras, and in view of the positive intradermal tests obtained we feel justified in our diagnosis of allergic purpura. The rapid response to Chlor-Trimeton in 12 mg doses daily is called to the attention of our readers.

REFERENCES

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46-68 Hollis Court Blvd.
Flushing, New York (Sacca)

Progress in Allergy

MISCELLANEOUS REVIEW OF ALLERGY LITERATURE

For the Year 1950

LAWRENCE J. HALPIN, M.D., F.A.C.A.

Cedar Rapids, Iowa

WITHIN the past year, it has seemed that the "miscellaneous review" has assumed a wider and more complex background. After considerable thought and application, the decision has been made that the general outline followed in previous reviews[37,38,39,40] would best serve the purpose and intent of the editors. In passing, this reviewer offers the hope that the many publications concerning endocrine influences upon the allergic state will eventually be covered in an individual review.

The application of allergy to general practice is an interesting and worthwhile presentation by Black.[4] He has shown that the basis of a large variety of syndromes, once thought to be the explanation of only a limited group of conditions, is now a broader picture. Emphasis is placed upon the necessity for men in all fields of medicine to become aware of the diagnostic possibilities and the importance of this specialty in each individual practice. The wide variation in the symptoms of allergy does not in the least tend to deny the common explanation of each syndrome—that of the vascular reaction. Black explains also that the vascular reaction is not the only mechanism involved in the allergic picture. Mention is made of the antibody-antigen reaction, production of histamine, and the constitutional variation from the normal. Because of the common pathologic changes in many diverse conditions, the internist, the pathologist, and the allergist are proposing that the allergic field be greatly extended beyond its present limitations. Black fails to see any reason why prolonged symptomatic treatment should supplant the accurate recognition of any common allergic syndrome. Specific and nonspecific measures to be taken are discussed in an understanding manner and presented in very readable form. His remarks concerning the drugs to be avoided and those to be employed in the care of the asthmatic patient can be recommended for review by the practicing allergist as well as by the general practitioner. That the diagnosis of seasonal hay fever is not limited to the allergist and his laboratory is brought out by Moore,[70] in a brief but thorough discussion of the management of seasonal hay fever. One important statement by this author is the advice that antihistaminic drugs will not replace desensitization therapy but will aid to control the symptoms on days when pollen counts appear high. This may seem to be routine to the allergist, but many general practitioners depend entirely upon the "new" drugs for most allergic symptoms regardless of type, location, or degree. Listed as causes of treatment-failure are faulty selection of pollens, poor judgment of dosage, deteriorated extracts, or the failure to recognize factors other than pollens.

Advice to the general practitioner is also ably given by Epstein[27] in the management of allergic dermatitis. Correct treatment is twofold, with the result that adequate local treatment is augmented by the knowledge of the allergic, psychological, and endocrine factors. He feels that antihistaminic drugs have not lived up to advance publicity in their ability to relieve the accompanying pruritus. Dietary management rather than skin testing is, in general, more successful in the atopic dermatitis problem. Though emotional factors do play some part, this author was of the opinion that the importance of this influence has been overemphasized in the last decade. The

role that infection, both primary and secondary, plays in the production of or the prolongation of atopic dermatitis or eczema is well presented by Epstein. This infectious element must be recognized if proper therapy is to be administered. Local therapy must be appropriate for the stage of the lesions. Wise advice is given not to overtreat but to use a few well-chosen remedies which have a low sensitizing index. Further discussion of the role of the general practitioner in the care of the asthmatic patient is presented by Thomas[112] in this same symposium. Specific and nonspecific measures are introduced and adequately covered by the author. Though each presentation for the care of the asthmatic patient emphasizes the contraindication of morphine, instances are still met by many of us wherein the moribund patient has been placed in such condition by the administration of this drug.

Kerr[59] defines the common cold as "an acute inflammation of the upper respiratory tract, chiefly of the nasal mucous membrane, which manifests itself by local and by more or less disagreeable constitutional symptoms." The presence of histamine in the secretions should in no wise be interpreted as a cause of the condition. Histamine is evidence of cellular injury, and the association with an evident eosinophilia does not necessarily make a diagnosis of an allergy imperative. He feels that the common cold is not generally contagious, however. The role of the antihistaminic drugs in the therapy of the common cold has been overpublicized and leaves much to be desired. The scientific evidence for the use of these drugs in this condition is stated to be exceedingly flimsy. It is his impression that the solution of the problem will result from closer co-ordination of effort between the allergist, the virologist, and the physiologist. Agreement with the above impression re the use of antihistaminic drugs in the treatment of the common cold is noted in the work of Shaw and Wightman.[99] Their study comprised the use of the drug in 443 students; a placebo was given to 215 and 2-phenylbenzylamino-methylimidezoline hydrochloride to 228 patients. Roughly 50 per cent of each group thought that some improvement was discernible from the medication. It was found that side reaction was reported by 10 per cent of those using drugs and by 15 per cent of those receiving placebos. The duration of symptoms was found to be essentially the same in both groups observed. Similar reports were made by Hoagland and his co-workers.[46] Little change was noted in the duration of symptoms, variation of reported side reactions, and suggested benefit regardless of the time of drug or control administration. A noticeable lessening of nasal secretion was observed in those using drugs.

The problem of allergy in the child is entirely different from that noted in the care of adult patients. The diagnostic as well as the therapeutic approach must be altered to suit the occasion and the patient. Bigler[3] states that anyone doing pediatrics in this modern day must have a working knowledge and awareness of allergy. The differentiation between an infectious process and an allergic one must be given prime consideration by the examining physician. The attitude of the parents must also be given some thought in this decision. Bigler thinks that the attending physician is capable of caring for the allergic child depending upon the severity of the symptoms, the duration of symptoms, and the complex features of the individual problem. Closer co-operation between the allergist and the pediatrician is needed than when adult patients are being diagnosed and treated. This author feels that prevention of the allergic state is really the initial phase of therapy. Above all, the parents should not be informed that the child will "outgrow" his allergic symptoms. With this the reviewer is in hearty agreement, for all too often allergic children have been neglected because of this attitude. Bigler believes that careful administration of foods to the infant will, in many instances, reveal allergic intolerance that can be recognized and will permit proper substitution or alteration of the diet. A discussion of the therapy of the acute allergic symptoms concerns chiefly the use of drugs in the relief of the asthmatic attack. The question of immunization procedures in the allergic infant brings forth advice against smallpox vaccination in the presence of an

acute or active eczema. Antitoxins made from animal sera should never be used without adequate sensitivity testing. In the experience of the author, pertussis or typhoid vaccines do not produce allergic reactions. He believes that the tonsil question can best be answered by using the same criterion for removal in both the allergic and nonallergic child. Clein[18] has also been concerned with the tonsil problem in allergic children. He has found that in practically all instances where the tonsils and adenoids grew back, an allergic basis for the original symptoms had not been recognized preoperatively. Frequent colds or a hard, dry, hacking cough were the major symptoms for operation in these cases of recurrence. Chronic nasal discharge, "frequent colds," so-called "sinus" infections, and regrowth of the tonsils and adenoids with the original symptoms should all be considered as contraindications for surgery until adequate allergy investigative procedures have been completed.

Chobot[16] and his group studied eighty allergic children to determine any abnormalities of encephalographic tracings and any influence upon such patterns that might be shown by the use of an antihistaminic drug. All the patients were given complete physical and allergic examinations. Of the total graphs recorded, fifty-four were completely normal and twenty-six were abnormal. The incidence of abnormal patterns was high (thirty-three per cent) in the allergic children, with similar percentages being found in the families of these children. Trimeton failed to alter the electroencephalographic pattern to any appreciable extent. They feel that the abnormal patterns in the family lend weight to the belief that as allergy is inherited so is the encephalographic pattern inherited. In this same vein of prophylaxis of allergic disease, Glaser[35] believes that this feature is the sole province of the allergist. Of necessity patients, particularly infants, with no apparent allergic disease, should be treated and watched in order that the initial symptoms and signs of allergic manifestations may be recognized. The same principles apply to the internist in the care of nonallergic adults. This author feels, in agreement with others, that the original allergic evidence in infancy is "colic," or some gastroenterological picture. Involvement of the skin and of the respiratory tract follow in parade-like order in many cases. The question of removal of tonsils and adenoids is again stated to be based upon the same conditions for surgery that are present in the nonallergic child. Consolation for the parents, and sound advice to all concerned, should be based upon a thorough knowledge of the complaints, findings, and prognosis—all of which can be determined in the usual instance by a complete physical examination subsequent to a factual history. Regardless of the severity of the bronchial asthma, the complication of heart disease is practically unknown. A thorough understanding by the parents of all instructions for their child's care is the responsibility of the attending allergist. He must not only explain his measures and views but, in most instances, must elaborate his reasoning for such points.

The recognition of drug allergy is stated by Sherman[100] to be an easy affair when the symptoms of such allergy are similar to those of standard allergic responses. It is when the picture is clouded with irreversible changes of arteritis, periarteritis nodosa, extensive parenchymal necrosis of the liver, and focal necrosis of the myocardium that the diagnosis of drug sensitivity becomes difficult. Confusion with infectious processes may also be encountered when the picture is based upon fever, leukocytosis, and rashes. The administration of the drug may be orally or parenterally. We are all familiar with shock symptoms following the injection of heterologous antiserum. The same conditions may be noted following the injection of liver extract, insulin, vaccines and other protein-containing products. Fatalities have been reported with the use of acetylsalicylic acid by the sensitive patient, and most allergists are familiar with the terrific asthma associated with such sensitivity. On the other hand, we all have seen those patients in whom a tablet of aspirin is a source of distinct relief to that particular patient with asthma. Urticaria and angioedema are seen with the use of many drugs. Of late years, the most common illustration is the delayed,

severe, serum-sickness type of reaction noted with sensitivity to penicillin. An elevated temperature may be the only symptom or sign of sensitivity to the sulfonamides, thiouracil, or the iodides. A skin rash in association with such fever usually alerts the physician to the possibility of drug allergy. Prophylactic testing prior to administration is possible for protein drugs, but no true, adequate method of testing for sensitivity has been introduced for nonprotein drug sensitivity. In this latter instance the antigenic activity is dependent upon the combination of the drug with the body proteins. Desensitization is rarely successful with nonprotein drugs.

Generalized allergic manifestations to insulin have been reported by Stone et al.[110] Urticaria was noted in two patients, both of whom were eventually desensitized by repeated injections of small doses of the drug. Paley[75] found that the use of recrystallized insulin decreased the number and severity of reactions in sensitive patients. Most of the reactions (91 per cent) in 147 patients were of the immediate type. Because of the spontaneous loss of local reaction with recrystallized insulin, this author was in favor of using this material wherever severe local or general reactions to insulin were encountered. Sherman[101] reports a patient showing evidence of allergy and marked resistance to insulin. Both features decreased while diabetic treatment was continued and Pyribenzamine was used to control the allergic manifestations. Sera during the first month of treatment showed evidence of a factor which neutralized the hormone activity of heterologous crystalline insulin, but not that of human serum. The author felt that this resistance was due to an antibody combining with an inactivating insulin. Other work is cited to suggest that such resistance may be hormonal in origin rather than antibody action.

As cited in the above paragraphs, some drugs possess a high degree of reactive, allergic response. Demerol is suggested by Cohen[19] to have a relatively low toxicity and thus is a fairly safe drug to prescribe. This opinion is based on one case report in which the patient survived the ingestion of 25 tablets of 50 mg Demerol. The report is somewhat qualified with the admission that perhaps the patient did not absorb the entire amount, inasmuch as vomiting may have expelled some of the drug before absorption could occur. It is the opinion of this reviewer that the administration of any drug, regardless of type or action, should be administered cautiously and watchfully to the allergic patient. The initial ingestion or injection may be the sensitizing dose for later reaction symptoms. Stansbury[109] has related the tale of the patient who was accustomed to use as much as 800 mg of Demerol daily by the intravenous route. This patient was an asthmatic who eventually was able to control his symptoms by other measures and found the desire for the drug not to be present. This speaks in some small measure for the lack of addiction to the drug, as the above administration (the patient was a physician) was prolonged over a period of several weeks. Sensitivity to medications is an interesting if often unpleasant, part of the practice of allergy. Mitchell and Vilter[69] report on the use of folic acid in the therapy of granulocytopenia due to thiouracil sensitivity. Following the use of folic acid the skin rash cleared rapidly with the discontinuation of the sensitizing medication. A trial later, however, by the intravenous method, produced no apparent reaction with the initial injection. A similar injection of 50 mg intravenously on the next day resulted in violent signs of anaphylaxis which responded to emergency measures. Sensitivity to liver extract injections is the subject of a paper by Cook.[2] He presents a plan to administer the liver extract in dosages gauged to meet the individual needs of the patient, with the drug being given at intervals of forty-eight hours rather than at less frequent occasions. This is offered in the light that attempts at desensitization using minute, gradually increasing dosages may be of some apparent benefit, with the symptoms of reaction tending to recur with a resumption of the original, convenient treatment scheduled. A reaction to heparin is described by Chernoff.[14] The drug was given to a patient who had never received it on any previous occasion. There had been no personal nor familial history of allergy.

In this instance, dyspnea, cyanosis, profuse perspiration, and blood pressure changes were noted within one minute after the intravenous administration of 5 ml of sodium heparin. Later, scratch and intracutaneous tests with beef and pork heparin gave good, positive reactions, while similar tests for beef, pork, and lamb gave slight reactions. Passive transfer testing was successful in the demonstration of antibodies in the sera for all the animal products.

Recently, there has been some favor shown to the use of intravenous procaine in a few, varied allergic conditions. That this procedure is not entirely without its danger is demonstrated by Schuff and Schuff.[94] Their patient had had no evidence of reactibility to twelve intravenous injections of procaine, but with the completion of the thirteenth, a mild chill and some respiratory embarrassment were noted. On the next occasion, three days after the introduction of the medication, dyspnea and other symptoms of asthma were noted. Relief was obtained with epinephrine. Though intracutaneous testing with the solution was negative, a similar reaction to the intravenous use of the procaine was experienced on re-administration one month later. Isenberger[51] states that procaine should be given intravenously in low concentration because of its rapid disappearance from the blood stream and its prompt hydrolysis. Though he feels that individual idiosyncrasy is not uncommon, true toxic reactions will be found due to the rate of administration, the concentration of the solution, and the total amount given. That severe manifestations of serum sickness in patients who are not relieved with antihistamines may respond satisfactorily to intravenous procaine is the contention of Schrum.[93] The procedure for the use of this drug in children may vary to some extent from the usual indications in adult patients. A preliminary skin test should be done, but a negative reaction, as shown in the above cited case, does not indicate lack of the possibility of reaction. The proper dilution for intravenous procaine is 0.1 per cent. The rate of administration is recommended as 20 to 30 drops per minute, with at least two hours required for 500 ml. Personal experience with this preparation has shown that even in adults relief of symptoms is seen with amounts much less than 500 ml. Almost dramatic relief in serum-reactions has been noted from as little as 100 ml to 150 ml. In case of extreme nervous system stimulation, sodium amytal by intravenous route will control such symptoms. Schrum recommends that the amount of procaine in children should be 125-250 ml for patients of two to five years of age. For patients of five to ten years, the amount can be increased to 250-500 ml. Amounts up to 750 ml of the above 0.1 per cent solution can be safely administered to children of ten to fifteen years of age.

At the 1950 meeting of the Southwest Allergy Forum in Memphis, Tennessee, considerable discussion was based upon the reaction experienced by many patients to the bite of insects, bees, and other "wild life." At that time, the impression was gained by this reviewer that most of the patients with such sensitivity must have residence in the southwest. But, as things will go, during the past year in a Midwest practice of allergy, no less than seven such patients have been seen, with some of them being extremely uncomfortable from the resultant symptoms. Edema, cellular infiltration, and necrosis of muscles are the predominant histological findings, as noted by Crewe and Gordon.[23] Inflammatory sequence is noted in older lesions. Ant bites are also the causative factors in some allergic reactions. Morhouse[72] describes a patient who had been bitten by ants with resultant itching, swelling, and urticaria. Cyanosis and shock did not respond well to epinephrine and oxygen, but relief was almost instantaneous with intravenous procaine.

Recognized or unrecognized allergy complicating various forms of heart disease and other cardiovascular symptoms is reported by Bernstein and Klotz.[2] A small percentage of their cardiac patients were found to possess evidences of allergy. The discovery was made either by history or by examination. Specific cases are reported. Most of these patients were found to have some aggravation of their cardiac symp-

toms when exposed either through diet or environment to the offending allergenic substances.

Fatalities as the result of skin test material may be more common than the literature reveals. Harris and Shure[42] could find only eleven reports of death resulting from the introduction of testing material. In each instance, the causative or suspected allergen was one of the materials possessing high allergenic activity—egg, glue, buckwheat, cottonseed, and others. These authors report another fatality due to the use of intradermal skin tests. Their patient had shown mild reactions to a few grass pollens which seemed to be the basis for further intradermal skin tests. These consisted of miscellaneous environmental substances. Death within ten minutes followed the introduction of these tests. The initial symptoms of shock occurred within one minute after the tests had been done. No positive skin reactions were determined prior to death. Passive transfer serum studies revealed the patient's serum to have contained antibodies for cottonseed, dust, orris, and perhaps pyrethrum. Serial dilutions of these positive reactors, again on passive transfer, suggested that the continued reactability of the cottonseed extract in 1:80 dilution was the antigen responsible for the fatality. Because of the lack of severe reactions with routine use of cottonseed extract intradermally, the authors believe that this feature verifies their point that constitutional reactions are due not only to the antigen but to an exquisite degree of sensitivity on the part of individual patients. This all may be true, but it must be remembered that there has never been a reported fatality nor a severe constitutional reaction from scratch test material. It is the opinion of this reviewer that any author with the courage—for that is correct—to report a fatality from an intradermal skin test, should have the patience to do preliminary scratch or puncture testing. In this way, extreme sensitivity possessed by some patients for highly antigenic substances will be safely elicited. Peshkin[77] states that he "has not encountered a single general reaction with the intradermal technique FOLLOWING (capitals mine) a properly performed, negatively reacting scratch test." Morse[73] has reported that a comparatively safe method of skin testing patients is the electrophoretic method. He has devised an apparatus permitting multiple testing in safe degree. He has found that several successive patients may be tested without the further addition of extracts to the cups and that these pads may be stored for several days between tests without the addition of extracts. Inasmuch as this method of testing uses the unbroken skin, a large number of pollen extracts may be applied simultaneously. The occurrence of many strong positive reactions will be noted; but in spite of this, constitutional reactions have never been observed nor reported. This author believes that though pollen, dust, and other inhalant extracts do respond with good positive reactions by this method of testing, food extracts have probably not been sufficiently concentrated to give dependable results by this method.

It is the common medical impression that the greatest majority of patients complaining of simple fatigue probably have their symptoms based upon some feature of psychosomatic origin. Meyer[67] felt that probably some patients with fatigue may have their symptoms founded upon an allergic background. The idea for this impression originated when he noticed that hay fever patients, in addition to their localized rhinitis, also complained frequently of utter exhaustion. This was true even though the nasal symptoms were well controlled with adequate pollen therapy. The same degree of fatigue could be noticed when pollen dosage was given in too great amount and a slight constitutional reaction resulted. In the same line, the patient with a definite food allergy has frequently complained of fatigue, more frequently than patients with other symptoms. Meyer also feels that seasonal variations in cerebral accidents, cardiovascular accidents, and various psychological disturbances do make one still more curious about the allergic etiology of these symptoms. The fact that he has been unable to establish any anatomical or pathological-physiological diagnosis is very definite. Davison[26] has investigated many patients with the com-

plaints of fatigue, but in these he was unable to demonstrate that simple sensitivity to inhalants was a definite factor. He was able to relieve many cases of fatigue by omitting some foods from their diet, particularly those to which the patient was sensitive in rather marked degree. Of these foods, milk was the most prominent offender. He is of the opinion that fatigue should frequently be classified as one symptom occurring in cerebral allergy. Rowe[87] feels that allergic toxemia may manifest itself by weakness and fatigue that is usually not relieved by a good night's rest. He believes that this allergic toxemia is usually the result of ingesting foods to which the patient is allergic. Often the allergic toxemia will be a complication of pollinosis. The complaints of fatigue may not necessarily be continuously present but may seem to occur in attacks similar to those characteristic of other forms of allergic disease. The fatigue may or may not appear with other symptoms of allergic disease. It is Rowe's impression that the definite diagnosis of allergic toxemia may be made only after the presence of other diseases has been excluded by meticulous physical examination, laboratory studies, and x-ray examinations. He is of the opinion that the use of elimination diets is probably the most efficient form of investigating this food allergy. This reviewer has observed a few patients in whom the complaint of fatigue was thought definitely to be upon an allergic basis. It is a well-established fact that most patients undergoing pollen therapy, particularly with the initial injections of such treatment, will complain of tiredness for a few hours or even a few days following the administration of their treatment dosage. In this same line—though it may not necessarily be true fatigue—Shilkret[105] has reported a case of a female patient complaining of violent and prolonged sneezing attacks associated with yawning. He felt that her complaints were upon a primarily psychogenic basis inasmuch as she was emotionally upset over the illness of her sister. No evidence of allergy could be observed, and a complete allergy investigation was negative in all respects. Her symptoms were controlled by suggestion, but a relapse occurred following the denial of compensation.

Keeney[57] discusses four classes of fungi. These are Basidiomycetes, Ascomycetes, Phycomycetes, and Fungi Imperfecti. Of these, the Ascomycetes are the largest class of fungi, including many plant pathogens as well as the molds which are important to the bacteriologist. The molds encountered for the most part by the bacteriologist and the clinician fall into the class of Fungi Imperfecti. The rusts and smuts are of the class Basidiomycetes, however, and thus prove an exception. Keeney's discussion is primarily directed to those fungi which do produce allergic manifestations. The discussion deals chiefly with those molds and fungi well known to most allergists as causative factors of respiratory symptoms. The pathogenic fungi are also discussed, and these primarily are familiar to the average physician. He feels that a positive skin test with the broth filtrate of one of the species of genus *Trichophyton* may be used in determining the presence of an infection with the *Trichophyton* fungi. A positive test only indicates that the patient has been infected either in the immediate or distant past with one of the *Trichophyton* fungi. A negative reaction does not necessarily rule out the possibility of any fungus infection. It simply means that the physician must be on the lookout for the various skin-sensitizing properties of various fungi in different patients. *Trichophyton* fungi play a role in the development of "spontaneous" allergic manifestations to penicillin. If mold sensitivity is suspected, it is not sufficient to study the mold content of the out-of-door atmosphere, but it also must be remembered that the indoor air must be studied for its contamination. Keeney deplores the routine testing for skin test type of sensitivity using a few commercial mold extracts without further clinical investigation.

In the past few years more attention has been given to the influence of the psyche in the production and aggravation of most symptoms of allergic disease. Zoss[123] reports a case in which the feature of anxiety plays a large role in the course of

an asthmatic attack. His patient, a nineteen-year-old young man, was first seen with a history of having had repeated asthmatic attacks for three years. The patient had been informed in a naval hospital that he had only two years to live. Anxiety resulting from this statement kept him in constant fear of his life. Complete allergy investigation by skin testing revealed good intradermal reactions to house dust, feathers, and *Alternaria.* Treatment with these extracts did bring fairly good results. Repeated attacks of very severe asthma could be controlled only with large doses of intramuscular or otherwise administered sedation. In one attack of asthma(?) the symptoms were of sufficient severity that a tracheotomy was done, and much relief was obtained with the aspiration of mucus from his trachea. (It has always been my belief that a tracheotomy would not ease the respiratory difficulty of *asthma.)* Following reassurance that a tracheotomy would always permit him to breathe in spite of any amount of mucus, the patient apparently recovered from his fear of impending death. The author has reported that the patient has not had a recurrence of his asthmatic attacks over a period of approximately two years. Clarke[17] considers the psychosomatic angle from a different aspect inasmuch as he has reported from the relation of allergy to character problems in children. One interesting feature of his paper is the response obtained to a letter written to several allergists in the United States. Of the letters sent out, 171 replies were received. None thought the allergic picture was completely divorced from the patient's personality. Seven took the attitude that allergy definitely was psychosomatic in origin, with the allergic disease resulting from emotional conflict between the patient-children and their surroundings. Of the 171 replies, fifty-eight thought that their attention had not been drawn to the psychic complications of allergy. Ninety-five were of the opinion that personality changes due to allergy did correct themselves when the allergic side of the condition was eliminated or treated. Clarke surveys twenty-four typical patients that are rather characteristic of definite character problems and personality changes. These twenty-four patients are chiefly those reported by the various men answering the questionnaire. He feels that if every problem child could be given the benefit of a complete allergy investigation, many of them would be found to be definitely allergic, with improvement being based upon proper allergic management of the hypersensitivity. Clarke feels that allergists should pay more attention to the psyche of their child patients. Blue[6] has also discussed the relationship of emotional disturbance to allergic manifestations. He reports that allergic diseases based upon psychogenic background can be classified to include those patients in whom specific somatic diseases are influenced by mental states. Three patients are reported. All of these three patients had definite allergies which were influenced by emotional conflict. Blue is of the opinion that there is a large psychogenic factor that must be considered in the management of allergic diseases, more so than in almost any other generalized field. Gunnarson[36] reports the comparative results in fifty-eight patients, twenty-one females and thirty-seven males. His data show the inheritance of psychic diseases to be just about parallel with the inheritance percentage of allergic diseases. The author cites several interesting instances in which the onset of asthmatic symptoms was definitely associated with an emotional upset or a serious conflict arising between the parents or between the parents and the patient. He notes that many asthmatic children display various neurolabile symptoms before the onset of the asthmatic complaints. Better treatment results in these patients are to be expected when combined somatic and psychic therapy is obtained. Schatia[92] has stated that a review of the literature will reveal the role of emotions in allergic diseases to be divided into four schools of thought. These primarily are based upon the division of opinion as to whether the personality problems are caused by allergy or whether the emotional upsets may initiate allergic symptoms in some specific patients. Another school feels that allergic constitution will parallel an allergic personality structure. Then there are those who state that allergic diseases are

entirely psychogenic in origin. The author is in agreement with those men who feel that the allergic constitution closely parallels an allergic personality structure. In therapy, Schatia states that the role of psychotherapy should be emphasized more than the simple relief of each individual or recurring attack.

Though no attempt will be made in this paper to review the subject matter of "The Allergic Informant," the attention of the reader is directed to this very interesting little booklet. Mulligan[74] has gathered together the answers to several questions sent to many allergists. To a great degree the questions are quite interesting, but the answers are even more so. In many instances there is direct opposition between two men answering the same question. In other instances, complete agreement is evidenced by the manner in which the questions are answered.

A simple apparatus consisting of a metal ring with two parallel bars crossing its widest diameter is a pollen-counting guide introduced by Credille.[22] This guide reduces the area of the field under active scrutiny without interfering with the diameter of the microscopic field. One advantage in the use of this guide is that all particles to be counted remain in the counting field for the same duration of time. No extra calculations by the technician are necessary in computing the pollen count. In the use of this apparatus, only the space between the two parallel bars is used as the counting field.

That the field of cosmetics is still one to be considered by the allergist in the care of his patients is emphasized by Whitacre and Parsil.[119] It is necessary to determine the actual exciting ingredient rather than to simply identify the certain cosmetic which is the sensitizing agent. Cosmetic allergy usually manifests itself in the form of a contact dermatitis, although many patients will show some respiratory symptoms due to cosmetic sensitivity. A thorough history is of the utmost importance in the identification of any cosmetic contact sensitivity. The authors list only five ingredients of face powder as being sensitizing agents. These are magnesium oxide, starch, tragacanth gum, orris root, and aniline dyes. Of these, the greatest number of reports have been made concerning the use of orris root in face powder. Most sensitizing reactions due to the use of face powder have been traced to perfumes or to the pigments used for effecting the desired shades. In the use of cold cream, it has been determined that the principal offender is probably lanolin or cocoa butter. In addition to these, perfume is also a common offender. Lotions, astringents, and tonics cause some irritation. This is probably not true sensitivity inasmuch as the contact distress is probably due to dehydration or defatting of the tissue to which the materials are applied. Nail polish sensitivity is very frequently encountered by the clinical allergist. The prevailing opinion at present seems to be that the principal offending agent in nail polish sensitivity is the synthetic resin which is used in conjunction with nitrocellulose. Recent evidence has been established to show that solvents and plasticizers are also responsible for much of the nail polish dermatitis that is seen. The authors warn against the indiscriminate use of hair dyes, rinses, restorers, wave sets, and various dyes used for eyebrow or eyelash cosmetic appearance.

The importance of fungi as causative factors of respiratory allergy has been emphasized by Walton.[115] Thirty-two per cent of 275 asthmatic patients showed definite clinical sensitivity to fungi. Thirty-six per cent of the total number of asthmatic patients showed positive reactions to skin tests with 1:1000 dilutions of the various fungus extracts. *Alternaria, Hormodendrum* and *Helminthosporium* were the most persistent and definite reactors. The author is in agreement with other mold investigators who feel that fungi are to be considered of major importance as causative factors of allergic symptoms throughout most of the United States. Bates[1] considers the accurate diagnosis of allergic rhinitis to be a difficult procedure. He depends mostly upon an accurate history, seconded by a nasal examination and microscopic examination of nasal secretions. Skin testing is also important. Other

examinations, as x-ray films of the sinuses and additional laboratory work, should be included in the diagnostic approach. Bates holds that though skin testing is important, the average physician usually places too much dependence upon this procedure. Principles of treatment depend entirely upon the avoidance of the offending allergens, wherever possible. In those instances where the causative substances cannot be adequately eliminated, a program of desensitization or hyposensitization must be considered. He holds the opinion that it is impractical for every patient to readjust himself by climatic changes when he is pollen sensitive. In most instances, specific therapy with pollen extracts with the use of antihistaminic drugs as adjunctives is the treatment of choice. The importance of general supportive measures in the treatment of the patient with nasal allergy cannot be underestimated. Harkness[41] has termed the story of the antihistamines and their development as "The Great Therapeutic Gold Rush." This author discusses the action of histamine in the presence of allergic disease and discusses the various antihistaminic drugs available on the market today. He presumes that the lack of knowledge concerning the metabolism of histamine has limited the use (and abuse) of antihistamines inasmuch as there has not been a firm foundation for investigative research. The fact that good results with antihistaminic therapy are not obtained in bronchial asthma is suggestive to this author that the positive factor is primarily not one of histamine antagonism.

Most allergists have long been familiar with the use of pollen extracts by mouth in the treatment of seasonal hay fever as well as the oral use of poison ivy extract in the treatment of this dermatitis. A very interesting publication by Black and Holman[5] concerning the use of dust extract by mouth in the treatment of respiratory allergy has been reported. Because the frequency of nonpollen respiratory allergy is much more marked than the pollen type, these authors began to use house dust as an antigen in the treatment of dust-sensitive children. All of their patients were under the age of thirteen years. It was felt that dust or pollen in each of these patients was a definite and primary etiological factor in the production of their respiratory allergy. Dust therapy by mouth was carried out with the same concentrated glycerosaline extract as that used for hypodermic therapy. The initial dosage was one drop on the first day. Each day showed a dosage increase of one drop until 15 drops were taken on the fifteenth day. The dosage of 15 drops per day was considered as a daily maintenance dosage. Black has found that it is unnecessary to initiate treatment with a dosage smaller than one minim of the 1:50 solution of concentrated dust or pollen extract. No constitutional reactions were reported from this amount, and relief of symptoms seemed to proceed as well as from dosages of a lower dilution. When an oral dosage of 15 drops per day was reached, if the patient had not obtained relief in this time, that dosage was continued daily for one further week. The hypodermic treatment was then advised and oral medication was stopped. This oral therapy was given to 402 children. Of these, seventy-three patients were considered to be only dust sensitive, and eventual results showed sixty-seven of these to be classified as obtaining good results. The dust-sensitive patients showed better results by far than did the pollen-sensitive patients on oral therapy. Of the total 402 treated, the authors were able to obtain adequate follow-up records on 294 of these for result evaluation. Of the 294, 221 patients had no treatment other than oral therapy with a single antigen, either dust or a specific pollen. They concluded that their results were good. However, hypodermic therapy gave satisfactory relief in a large number of those patients who did not obtain relief by the oral method.

Kurtz[61] makes an analysis of 610 females and 433 males with bronchial asthma, as compiled by the New York City Department of Welfare. During the first decade the incidence of asthma was higher in the males than in the females with the ratio being about three to two. Between the ages of twenty and fifty, about four times as many females as males were found to have bronchial asthma. The author is of the opinion that this may be a suggestion that hormonal factors play an important

part in the initiation of the asthmatic symptoms. Cardiac diseases were the most frequent complications of the bronchial asthmatic symptoms, with the occurrence of this state being present in about 12 per cent of the reported patients.

A very interesting study of the clinicopathologic findings in bronchial asthma is reported by Winer, Beakey, and Segal.[120] These authors studied forty-six patients. Thirteen of these forty-six died during an acute attack of bronchial asthma. The duration of symptoms had been from one month to fifteen years. Evidence of definite extrinsic allergy was found in only one patient and considered to be uncertain in another. The majority of pathological findings in these thirteen patients were consistent with those previously described by various other authors. Emphysema of moderate-to-marked degree was present in most of the cases studied. Areas of atelectasis were noted in only one patient, a six-year-old boy. Mucous plugs, however, were marked in almost all patients. The authors find that hyaline thickening of the basement membrane of the medium-sized bronchi, hypertrophy of the muscles of the medium-sized bronchi, mucous plugs in the bronchi, eosinophilic infiltration, sacculation of the bronchi, and excessive production of mucus are all necessary for the pathological diagnosis of bronchial asthma. Four of their patients with uncomplicated bronchial asthma showed definite hypertrophy of the right ventricle in the absence of hypertensive or valvular disease. The authors also studied sixteen patients who died with diseases which frequently accompany and are possibly related to severe bronchial asthma. Clinical findings varied from emphysema, bronchitis, bronchiectasis, bronchial pneumonia, and cor pulmonale. Thickening and hyalinization of the basement membrane were seen most frequently in the group of patients described under this heading. Where death was the direct result of intercurrent disease rather than bronchial asthma, these changes seemed to be related to chronic inflammation rather than to the true asthmatic background. The presence of eosinophiles was not as marked in these patients as in the former group dying in a true asthmatic attack. Seventeen of the forty-six patients expired as a direct result of intercurrent disease rather than asthma itself. The major anatomic cause of death in this group was lobar pneumonia. Pathological review of the patients who died of intercurrent disease failed to reveal any pathognomonic findings characteristic of bronchial asthma. Most of these patients did have pulmonary emphysema, but the other necessary findings were not available. These patients did not have thickening of the basement membrane, nor was hyalinization present in any degree. The authors also present very interesting and graphic pathological plates. That there are other factors in asthma besides allergy has been re-emphasized by Rackemann.[78] He described what is classified as extrinsic and intrinsic asthma. The feeling persists with this author that intrinsic asthma occurs after the age of forty and seldom is to be considered as allergic in origin. Intrinsic asthma is quite often seen in younger patients, but all too often the term "intrinsic asthma" is given to those patients for whom no extrinsic cause can be determined. Rackemann considers the intrinsic asthmatic patient to have inherited a basic factor which is otherwise unknown but does seem to set the stage for asthmatic symptoms. The effects of stress and strain seem to predispose some of his patients to various forms and symptomatology of allergic disease. It is the impression of this reviewer that discussion between the presence or absence of an intrinsic asthma can best be summarized by pointing out that infection associated with some form of bronchial obstruction is usually the chief etiological factor. That weather plays a large role in the production of asthmatic symptoms, particularly as far as frequency and severity are concerned, has been emphasized by Rosen.[86] Changes in the outdoor weather did seem to cause some increase in the severity and frequency of asthmatic symptoms, even though the patients were hospitalized and their indoor weather changed but little. It is emphasized that a decrease in temperature associated with a similar decrease in humidity are important predisposing factors. Rosen states that perhaps the weather changes do

influence absorption of allergens from the nasal mucosa. In a persistently low area of humidity the drying effect upon the nasal mucosa may make it more permeable. Weather changes may produce more susceptibility to infectious colds. Thus secondary attacks and symptoms of asthma may result therefrom. This reviewer has several patients who seem to follow the barometer regardless of whether their usual attacks have been adequately controlled with specific or nonspecific measures. These "barometer patients" seem to be almost infallible in their predictions of weather changes.

The presence of respiratory allergy in infancy is not an uncommon occurrence. In fact, Ratner[82] judges this to be the commonest of all childhood allergic manifestations. He believes that the diagnosis of asthma can be made only upon the basis of repeated attacks of shortness of breath associated with sonorous and sibilant râles. As contrasted to respiratory allergy in the adult, skin tests in an attempt to find the causative factors should not be made until such time as the skin has become sensitized. In this same light, as contrasted to the adult patient, foods play a large role in the production of respiratory symptoms of allergy in children. Inhalants and contacts have parallel importance as far as causative substances are concerned. Ratner regards epinephrine 1:1000 as the drug of choice to be used in the treatment of childhood asthma with the dosage being small, preferably three to four minims. He does not condone the use of epinephrine by inhalation because the dosage cannot be adequately controlled. Morphine, atropine, antihistamines, Demerol, and large doses of ephedrine are contraindicated in childhood asthma. He also recommends the use of bronchoscopy whenever the removal of thick, tenacious bronchial plugs cannot be adequately obtained with other measures, namely, the use of an emetic. Miller et al[68] have reported a simple, safe bronchographic technique for children. The patients are prepared in the routine way by the administration of atropine, morphine, or Nembutal in suitable dosages. Topical anesthesia is obtained with the use of 0.5 per cent Pontocaine. This solution is given by inhalation of aerosol. Lipiodol is then passed through a short catheter, and because of this adequate anesthesia, there is very little coughing, gagging, or swallowing of the material. The lipiodol is then permitted to flow into the various segmental branches of the lungs. Postural drainage for thirty minutes is begun immediately after the x-rays have been obtained. Nine deaths in 151 patients admitted to the hospital with a diagnosis of "wheezing chest" have been reported by Schwartzman and Nau.[96] In three of the nine patients, death was found by autopsy to have been due to bronchopneumonia. Two of the deaths were due to miliary tuberculosis, and one was caused by nephrosis with pulmonary congestion. All of these patients, however, were studied from the standpoint of rather marked wheezing in their chests. Fifty-five of the original 151 hospital admissions had a positive history of allergy. Most allergists have seen patients who were said to have "outgrown" their asthma or have been questioned by mothers as to whether their children would "outgrow" the disease or not. Metzger[66] studied the records of four thousand asthmatic patients to arrive at a very definite answer in this interesting problem. The greatest number of remissions occurred in patients twenty to thirty years of age. There seemed to be no apparent difference in the duration of the remission and the age at which it occurred until the fifth decade was reached. After that time remissions were much less numerous but were definitely shorter in duration. Freed[32] studied 160 children ranging in age from one to twelve years of age. All of these patients had irreversible bronchiectasis. In 55 per cent of these patients pneumonia was associated with the onset of symptoms, or the initiation of symptoms was subsequent to an attack of whooping cough. Asthmatic symptoms were noted in 33 per cent of the patients studied. Bronchography was the most important diagnostic single procedure, whereas bronchoscopy was not of any benefit as a diagnostic aid nor in the localization of the bronchiostatic process. Waldbott et al[114] have concluded that irreversible bronchiectasis is very rare in bronchial asthma if it does exist at all in association with this allergic disease. They have suggested the term pseudo-

bronchiectasis, indicating that this is a reversible process upon an allergic background for which surgery is not indicated.

Waxler and Schack[117] have revealed that both the size of the dose and the route of administration seem to influence the concentration and maintenance of aminophylline in the blood stream. The intravenous administration of 0.25 grams of aminophylline produced the highest mean level of 600 micrograms with a progressive fall after about nine hours. The intramuscular injection of 0.5 grams produced a mean level of only 326 micrograms although the significant sustained level extended over a period of thirteen hours as compared to the above nine. With lower dosages, the levels were persistently less and remained at a good degree of blood stream level for a shorter duration of time. Uncoated tablets were absorbed more regularly and produced higher blood levels than did enteric-coated tablets. The instillation of rectal suppositories produced variable findings. Some patients failed to show any blood level of aminophylline whatever after the instillation of the rectal suppository. This reviewer wonders whether this might not be due to the use by these patients of some form of mineral oil by mouth. It is a recognized fact that aminophylline rectal suppositories will not be absorbed if the patient is using mineral oil or some other form of oil laxative. This is also true if the suppository has been coated with soap, oil, or some other substance to make introduction easier. The therapeutic action of aminophylline is probably related to its blood stream level inasmuch as the drug is slightly bound to protein and is restricted to its presence in the plasma.

It has long been recognized that the sensitizing powers of substances do vary and that individuals possess variable degrees of sensitivity. The skin of different persons and of even different portions of the skin of the same person respond in singular manner to both primary irritants and sensitizers. The above is not only true but it can be accepted that an individual may vary from time to time as to his reactibility to various substances. The patch test had never been standardized prior to the work done by Schwartz.[95] In explanation of the need for a standardized patch test, this author recognizes the fact that the reaction to such a method of testing depends upon the degree of the patient's sensitivity as well as upon the concentration of the substance applied. Other factors to be considered are the amount of the substance applied per square centimeter of skin and the length of time during which it remains in contact with the skin. All of these features have been adequately controlled by using a piece of flannel measuring three square centimeters which becomes saturated with 0.2 cc of a specified liquid. The pipette used to measure the amount of liquid is a graduated aid. This test is then further insulated with a square piece of uncoated, regenerated cellulose, one to one and one-half inches on each side. A piece of elastoplast of a special shape measuring three inches across the diagonal is then applied. The piece of cellulose adheres to the center of the elastoplast, and the piece of flannel is attached to the center of the cellulose. In this way comparative tests can also be determined on the same patient by placing patches of similar concentration on them or by placing patches of different concentration on the same patient for comparison. Ointments can also be tested by this standardized method by spreading definite amounts over the surface of the three-square-centimeter piece of flannel. Siegel and Meltzer[106] prefer what they term "usage tests" as more reliable than patch tests. They base this opinion upon the performance of 200 routine patch tests on a similar number of patients. Their testing material was Sopronal ointment or powder. The patients had never been in contact with this material prior to the patch testing. All the materials caused primary irritation upon the initial testing. However, two weeks later the patients who had primary irritation reactions showed negative reactions when retested. Even some of those who responded with positive reactions on the second test had shown negative reactions following the initial test. There was not a single reported instance of dermatitis following the subjection of these two hundred patients to usage tests which covered a period of one week. The

authors thought that the volatile substances probably produced reactions of irritation rather than true contact positive patch test recordings. Holland et al[49] could not determine whether a material was a primary irritant or a definite sensitizer when they considered the sequence of reactions or the severity of each individual reaction. They tested a series of military personnel with fourteen thousand "prophetic" patch tests. Because the number of reactions seemed to be greater than expected, particularly during hot weather and when the Schwartz adhesive patch test was used, the authors substituted a nonadhesive elastic bandage. They also used AIHL patch of elastic adhesive tape without cellophane backing, leaving an adhesive-free, porous center. The number of reactions using these latter two methods of testing were only a fraction of the number obtained from the same material with the Schwartz patch. The reactions were also less severe.

Kalz, Bower, and Prichard[55] report a very interesting case of dermographia. Their patient had had persistent dermographia, originating in 1936 following a widespread dermatitis of unknown origin. This patient had had an urticaria which had not seemed to be associated with any ingestant or emotional upset. Friction of any kind, however, would produce urticaria at that point with a persistent presence of about twenty-four hours following a latent period of six to eight hours of freedom. All forms of allergy investigation were negative in testing except that the dermographic reaction did occur at the site of test after the usual latent period with the usual persistence of about twenty-four hours. Nerve blocking with procaine did not alter the severity of the subsequent reaction following tests. Definite and marked clinical improvement was noted following the systemic injection of small doses of histamine phosphate intradermally. The influence of sweat, heat, friction, pressure, and tension all are points brought out by Gaul and Underwood[34] as factors that must be considered in discussing irritation or sensitization from footwear. Many of the polishes, solvents, adhesives, and various fabrics used in making shoes are definite irritants or sensitizers. These authors made extensive studies on 160 cases of dermatitis during which time 350 shoes were destroyed and patch tests performed from the materials. The water-repellent properties of some footwear seem to predispose the feet of a few patients to various fungus infections as well as to various forms of contact dermatitis.

The treatment of poison ivy dermatitis has long been a debatable point among dermatologists and allergists. At one time this reviewer was of the opinion that poison ivy extracts should be used in therapy of patients in the acute stages of the dermatitis. Since then, however, application has been made in the "I-wish-I-had-never-said-that" club. The opinion is now held that the use of poison ivy extract in the active lesions of poison ivy dermatitis is definitely contraindicated. However, its use in prophylaxis is well understood. Hoagland[47] used a poison ivy extract in three groups of patients at a summer military camp. Sixty-six per cent of twenty-one injected subjects were affected, and 83 per cent of twelve untreated controls developed poison ivy dermatitis. In another group, dermatitis was noted in 50 per cent of thirty-six treated patients who had not previously been seen by the author, but of whom 34 per cent did give a history of having had poison ivy dermatitis in the past. Only 24 per cent of twenty-one patients later developed poison ivy dermatitis. Unfortunately, the author does not give his schedule of dosage nor the type of extract that was used in prevention. No comparison is made between the severity of treated patients with the severity of their lesions prior to the institution of such prophylaxis. Gaillard[33] treated a total of 113 patients with an aqueous alum precipitated pyridine ivy extract over a period of three years. Patch testing on thirty-six of these 113 patients with serial dilutions of alcoholic and pyridine extracts demonstrated that a lesser dilution of the latter ivy extract was required to elicit a positive reaction. Higher dosages could also be obtained with this extract, and the dosage schedule could be completed more rapidly. Seventy-seven per cent of the total patients treated

obtained satisfactory results during the first season of treatment. Forty-six patients were treated for two years and 84 per cent of these had success in the second year of therapy. The third season of treatment produced good results in twelve of thirteen patients treated for the total of three years. Keil[58] concerns himself with the alleviation of the acute attack. The material used was 3-n-pentadecyl catechol, given by the intradermal route. Twenty-seven attacks of poison ivy dermatitis were observed in twenty-five patients. The most satisfactory concentration used for treatment was found to be a dilution of 0.001 per cent of 3-n-pentadecyl catechol in sterilized peanut oil. The treatment schedule ranged between 0.1 and 0.3 cc with the average dosage and the most optimal one being 0.2 cc repeated in forty-eight hours. No local treatment was recommended nor used other than the occasional drainage of large bullae. No constitutional reactions were encountered. There was slight induration and itching noted at the sight of injection in some instances. The author found that there was relatively rapid lessening of subjective symptoms and a definite shortening of the course of eruption. Six illustrative cases are described.

Sherman and Cooke[102] report three cases of dermatitis following the use of Pyribenzamine and Antistine. In two cases the causative substance was Pyribenzamine ointment, and in the other Antistine eye drops were incriminated. In one patient with a skin rash produced by Pyribenzamine ointment, the lesions continued with oral use of Pyribenzamine tablets even though the ointment had been discontinued. Positive patch tests with pure powdered Pyribenzamine were very definite. One patient showed positive patch test reaction to three antihistaminic drugs which have a common structure but did not show positive patch test reactions to other drugs of the antihistaminic group which have different structures. Their third patient did not show a reaction to Thephorin, although she did show definite reactions to eight other antihistaminic drugs which had considerable variation in chemical structure. Thephorin differed markedly from the others of the reactive group. This reviewer can recall a patient seen by him within a period of the past year. She had a very definite contact dermatitis around her eyelids due to the use of Antistine eye drops during the recent hay fever season. The lesions were marked and of rather prolonged duration considering the knowledge by the patient that the use of these eye drops did produce an exacerbation of her lesions. Good clearing followed the removal of the eye drops from her treatment schedule. Subsequently definite positive patch test reactions were obtained with the material.

Evans and Johnston[28] report upon a series of 159 cases of chronic urticaria and angioneurotic edema observed during a two-year period. Etiologic factors were described showing possible drug factors as being high on the list for cause. Psychogenic factors were considered to be the greatest single item, however, with 63.5 per cent being so classified. Twenty-nine per cent gave a history of constipation, which was felt to be causative of some urticaria. Focus of infection was listed as 26 per cent. Fifty-five of these patients were given skin tests, with fifty-four instances of significant reactions to various allergens. No single therapy was found to be beneficial in all instances.

Sherman and Seebohm[103] report a series of studies of a patient with cold urticaria. This patient's serum was readily transferred with its sensitivity to normal skin. The application of an ice cube to the skin of the forearm for ten seconds produced a definite urticarial wheal which developed within eight minutes of the removal of the ice. Exposure for two seconds to the ice had no visible effect upon the skin. Longer contact than one minute did not produce any greater response than reasonable periods shorter than this time. The effect of antihistaminic drugs prior to the application of the ice produced no change in the degree of reactivity. Passive transfer tests were done. Within five minutes of the removal of the ice a definite wheal without pseudopod formation or itching appeared at the site of the patient's serum. The

control site showed no reaction. The skin-sensitizing activity of this serum was only slightly affected by mild heat. The skin-sensitizing activity, however, was destroyed by heating for four hours at 56° Centigrade. By electrophoresis, four fractions were separated from the serum. These contained albumin, albumin and alpha globulin, beta and gamma globulin, and gamma globulin. The authors regard more than one protein component to be necessary to produce sensitization, inasmuch as mixtures of all four fractions or of beta and gamma globulin sensitized normal skin.

Inadequate recognition has been given to patients with food allergy and symptoms that are derived therefrom. Allergists today are familiar with the many writings and investigations that have been published by Rowe, Rinkel, and Randolph. Most allergists also recognize the fallibility of diagnostic work done with present-day food extracts. Some men depend to a great degree upon the reactions produced by either scratch or intradermal skin tests. Even they finally make their decision as to whether a true food allergy has been present or not by placing the patient upon an elimination diet. In this way, it is proven that an adequate trial diet is the only means by which food allergy can be studied and gradually controlled. Rowe[88] believes that food allergy may occur at any time of life, having its onset even in old age. He does not rely to any great degree upon skin testing, because positive reactions too often are due to potential allergy or nonspecific causes. In reviewing 1500 co-operative patients with bronchial asthma, food allergy was found to be the sole cause in 40 per cent up to the age of five years. Asthma based on food sensitivity was noted in 20 to 40 per cent in the other age groups, even over fifty-five years of age. Rowe has depended to a great degree upon the cereal-free elimination diet when studying a bronchial or nasal allergy patient. The fruit-free elimination diets are usually used when the patient with gastrointestinal or urogenital complaints is the object of study. The trial diet must be continued until the symptoms have been absent for two to three times as long as the usual periods of former relief had been noted. Children will often regain almost complete or partial tolerance with the exclusion of foods for which they have a definite sensitivity. This will usually occur within one to three years and the use of these foods may be permitted after the time without any symptoms being derived therefrom. Lee and Squier[62] write that provocative diets provide a method for the determination of a food sensitivity, particularly in adult patients. They feed their patients a diet consisting of wheat, milk, egg, beef, orange, and potato exclusively for about one week. In this way, they are able to determine whether there has been any food intolerance during childhood, since excessive ingestion of any of these six major foods would re-establish specific intolerance that had been present or would bring to light a latent sensitivity. If the patient does not have an exacerbation of his symptoms with the above six listed foods, the physician is then aware that the diet may be enlarged from this point onward. The use of provocative diets in the recognition of a good allergy is simply the elimination diet in reverse order. With the use of the elimination diet, the physician makes an attempt to eliminate those foods which may be suspected as causative of symptoms. In the provocative diet, the physician makes the attempt to really cause symptoms by the feeding of suspected foods. Rowe[89] has published standardized elimination diets which contain those foods which infrequently cause allergy. These were first published in 1927 and have been changed very little since that time. The fact that these elimination diets have withstood the so-called ravages of time would lend a good degree of value to their use by the average physician and allergist in his search for food allergy. Variations are obtained by the addition or substitution of various cereals, fruits, or other foods to the diet as listed by Rowe in his publications. Food should be excluded for which allergy is suspected and/or for which a definite dislike is admitted by the patient. Also, those foods which have shown large positive reactions on skin testing are excluded by the elimination routine. It must be remembered that it is not sufficient simply to give the patient a list of foods that are to be avoided.

One of the most important features of the elimination diet provides the patient with a list of the foods that *can be used,* insuring his nutrition as adequate and satisfactory in all respects. After relief has been obtained for a period of time sufficient to prove the worth of the elimination, individual foods are added. Each food should be taken for a period of three to five days before the addition of any new substance.

The treatment of food allergy in infants and children must combine the removal of the foods for which the patient is sensitive with the principles of good nutrition. Jones[53] concludes that scurvy, rickets, and anemia may be produced by poor assimilation of essential food elements. These elements are supplied ordinarily by the foods for which the patient might be sensitive and, therefore, the diet would be inadequate in these respects. If the patient has a sensitivity for any of the foods providing vitamin C in the diet, those foods must be removed and adequate substitution be made so that the infant or child will still be in good health. The recognition of an allergy is an important feature that must not be overlooked. The author deems the real test for a diagnosis of food allergy to be the elimination of the food in question with improvement in the patient's symptoms. Later trying that food and producing definite symptoms as had been noted on a general diet provides confirmation. Ingelfinger[50] and his co-workers state that a definite diagnosis of gastrointestinal allergy must meet the criteria as follows: the cause of the symptomatology must be found by contact with a definite substance that is innocuous to the majority of the population; there must also be evidence of immune mechanism available, and demonstration of definite functional changes must be made in the gastrointestinal tract. Diagnostic methods have not been sufficiently accurate to permit all patients with a diagnosis of gastrointestinal allergy to meet the above criteria. Symptoms characteristic of gastrointestinal allergy may be common to many conditions and to many patients. Lichstein and Benjamin[63] describe the changes in the interior of the stomach as observed by gastroscopy in a patient with bronchial asthma and urticaria. Gastric edema was transient and cleared with the use of adrenaline. Observation of the phenomenon was made through the gastroscope. They recommend that the gastroscopist consider allergic edema or allergic gastritis when bogginess, hyperemia, and hypersecretion of mucus are encountered. Zindler and Colovos[122] report anthocyaninuria following the use of beets by individuals sensitive to this food. Twenty-eight cases are reported, with twenty-six being associated with beet allergy. The pigment in the urine of two of these patients seemed to be related to allergic reactions to other foods. Their criterion for the diagnosis of beet sensitivity in their patients was the production of clinical symptoms following the experimental feeding of beets. These individuals had previously avoided this food and beet sugar for a period of four days; the test feeding was made on the fifth day. They are of the impression that anthocyaninuria is a valuable aid in the diagnosis of beet allergy. Some of these patients were able to maintain freedom from their symptoms while using beet sugar but still had to eliminate beet from their diets. The old argument as to whether a patient is sensitive to edible oils or not is again given some thought by Rubenstein.[90] He describes a thirty-one-year-old male patient with symptoms of nausea, vomiting, weakness, and generalized erythema following the ingestion of sesame seed or oil. The author states that an intracutaneous test with an extract of sesame seed produced a marked positive reaction. This reviewer wonders whether the author might not have been more conservative to have tested his patient by scratch method of testing.

A general discussion of food allergy based upon twenty-five years' experience is well worth the reading by anyone interested in allergy. Kahn[54] states that while eczema, dermatitis and various other sequences of food allergy are usually ascribed to food sensitivity, many of these conditions may be due to contact. Some forms of dermatitis, headache, and other symptoms usually ascribed to food allergy may also be due to an inhalant sensitivity. The absence of any positive skin tests or of any improvement upon elimination or provocative diets should lead the allergist to a

consideration of nondietary factors. Kahn is of the impression that skin testing is extremely valuable and should be made a routine procedure in the investigation of any food allergy. It is his impression that scratch testing should be done as a preliminary index of safety for subsequent intradermal work. Scratch testing excludes the possibility of any unsuspected allergen, as flaxseed or cottonseed, producing a constitutional reaction because of a high degree of antigenicity. He states that it is very rare that a dietetic item of clinical importance is found to produce symptoms of bronchial asthma. A common cause of failure in food allergy is the lack of recognition of the deleterious effects of drugs other than antihistaminic preparations. In his experience, the patient sensitive to cereals is usually sensitive to many grains. He has been unable to substitute any one cereal for another. All cereals are omitted from the diets of his patients when they are found to be cereal-sensitive. He advises that well-done, crisp Melba toast made from plain (not whole wheat) flour, oven-heated for twenty-five to thirty minutes, is an excellent practical substitution for bread. Some form of food diary is essential in the complete and successful investigation of the patient with a food allergy.

Moore[71] has stated that the migraine syndrome may be caused by allergic reactions, endocrine dysfunctions, disturbed fluid balance of the body, changes in blood volume, toxic metabolites, psychogenic causes, fatigue, and tissue bubbles in the brain occurring in decompression sickness. The first impact of this stimulus results in vasoconstriction, with a secondary vasodilation. It is during the latter phase that the pain of migraine appears. He raises the question as to whether the term "abdominal migraine" should not be changed to "abdominal epilepsy." The use of anticonvulsant drugs and measures is the method of choice in giving relief to patients complaining of these abdominal symptoms. Antimigrainous drugs will afford no relief because these medications affect dilated blood vessels.

Randolph[79] cites illustrative cases to demonstrate the importance of "inert ingredients" as causative factors of allergic reactions. The major excipients used for binding pills and tablets include corn starch, milk sugar, gum acacia, gum tragacanth, licorice powder, flour, sugar, and various chemicals. Corn is the most widely used in pharmacy of all these inert ingredients. All of the above-mentioned materials must be either suspected or proven as causative factors of allergic symptoms. They all must be borne in mind. Randolph states that gelatine, previously thought to have been nonantigenic, has caused definite reactions in beef- and pork-sensitive patients.

A review of the literature during the past twelve months has failed to reveal any new or startling findings in the diagnosis or treatment of migraine. Cohen and Criep[20] reviewed a series of fifty patients with complaints of chronic vascular headaches. All of these were given a trial with Cafergone. Forty-four of their patients had typical migraine, four had heaches classified as allergic in origin, and two patients had histaminic cephalalgia. A course of treatment was considered to be six tablets, each containing 100 mg of caffeine and 1 mg of ergotamine tartrate. The course could also be given rectally with three suppositories, each containing 100 mg of caffeine and 2 mg of ergotamine tartrate. As in former surveys, these authors found that the drug Cafergone was best used during the period of aura rather than after the attack had definitely begun or had reached its height. They have assumed that the beneficial effect of the caffeine and ergotamine tartrate is due to a synergistic action of the caffeine because of its vasoconstrictor or diuretic effects. The use of the Cafergone by mouth or by rectum does permit many patients to obtain relief without the use of hypodermic injections of ergotamine tartrate. The beneficial effect of ergotamine tartrate in migraine is probably due to the constricting effect upon the cranial arteries. Sperber[108] reports upon the beneficial effect of epinephrine in the treatment of migraine. His patients had failed to show any satisfactory response to any type of medication that had been used. Almost complete relief followed within five minutes after the administration of 0.012 cc of 1:1000 solution given sub-

cutaneously. Epinephrine on three successive occasions aborted the attacks of migraine of which one patient complained. His second patient received relief with 0.25 cc of epinephrine 1:1000 solution. The medication in this second patient was not of any value if it was given late during the course of the attack. A total of eight patients with migraine received relief from the small dosages of epinephrine. In six of them, Sperber thought that the medication was more satisfactory than ergotamine. No unpleasant side effects were noted from these small dosages of epinephrine.

The typical sensitivity for penicillin is very similar to that of serum sickness. The usual onset of the classical clinical symptoms is noted about seven to fourteen days following the administration of the antibiotic. The symptoms subside when the antigen titer decreases and the antibody titer of the blood increases. Keefer,[56] in a very interesting discussion on antibiotics, has stated that the reactions occur most frequently in patients who have had several courses of penicillin. Sensitization for penicillin is quite common following the use of the drug as an ointment, when it is instilled into the conjunctivae and when it is given parenterally. The oral use of penicillin is productive of the least amount of reactions. Because of the reaction in the skin at the site of previous fungus infections following the injection of penicillin, Keefer feels that there is a definite relationship between the penicillin and certain strains of *Trichophyton*. Some patients become sensitive to the vehicle in which the penicillin is held, whereas others do become sensitive to the penicillin itself. The future use of penicillin is not precluded in those patients whose degree of sensitivity is local. The patient may have no reaction following a second course or second injection. However, in some instances, the reaction may be accelerated in its appearance. It is safe to state that the longer the interval between the first and second injections of penicillin, the less likely the possibility of reaction. Any attempt at desensitization for any drug sensitivity has proven to be wholly unsatisfactory. Felder and Felder[30] have reported an interesting and unusual reaction to penicillin. This fifty-three-year-old patient presented serum sickness type of reaction following the first of four injections of penicillin. Blood chemistry studies revealed suggestive abnormal liver function. A four-plus precipitin reaction to *Trichinella* was also observed. Relief was obtained with the use of intravenous procaine, instituted approximately two weeks after the onset of the reaction. The presence of the *Trichinella* precipitin reaction was not considered to be specific for infestation inasmuch as this does occur in some cases of periarteritis nodosa and other forms of vascular allergy. Boelter and Hatoff[7] have reported a rather typical Shwartzman type reaction in a ten-year-old female patient. This young lady had been given penicillin-in-oil for a period of nine days. On the tenth day the medication was changed to aqueous penicillin. After two or three doses the patient complained of intense itching, developing sixteen to twenty urticarial wheals upon her buttocks. Each of the wheals surrounded a site where the penicillin-in-oil had been administered. Recovery from these reactions followed the discontinuation of the penicillin. Sanchez-Cuenca[91] has reported a patient suffering from a lung abscess from whom it was possible to make a culture of *Penicillium* from both the sputum and the feces. He felt that his patient was not only sensitized to penicillin used in treatment but was also sensitive to the metabolic products of the mold *Penicillium*. The continuation of this urticaria long after the discontinuation of the drug would tend to corroborate these opinions. A few patients who were treated with penicillin by Falk and Newcomer[29] were thought to have been sensitive to beeswax, as no other definite agent could be determined. Two patients showed transient pulmonary infiltration characteristic of Loeffler's syndrome. Eosinophilia was established as 44 per cent and 37 per cent in the two patients.

In a discussion of the host and infection in rheumatic fever, Watson[116] believes that this is a familial disease and that susceptibility to it is probably inherited. Attacks of rheumatic fever are usually induced by preceding group A hemolytic streptococcal

infections. In other words, before a patient can develop rheumatic fever, he must first have had a group A hemolytic streptococcal infection and again he must be a susceptible person—susceptible to that type of infection. It is Watson's opinion that the infectious elements could be controlled inasmuch as the susceptibility of the host is rather a constant inherited factor. Fischel[31] agrees with the above opinion to a great extent but adds that rheumatic fever patients do not show increased incidence of allergy in themselves or in their familial histories. Though many skin-sensitizing antibodies for *Streptococcus* have been found in rheumatic fever, none of these responses have been specific in differentiating between rheumatic and nonrheumatic type of infections or individuals. Specific desensitization with hemolytic streptococcus has been of very doubtful value.

Weille[118] has reported that sinus surgery resulted in a permanent cure in 10 per cent of the asthmatic patients that he had seen in practice. Good improvement for a period of at least two years was noted in about 50 per cent of the total. In 234 cases, nasal and sinus surgery produced 74 per cent good results. This author did not feel that any prediction could be made as to the benefit to be received from the operation. It is his opinion that the nasal passages can be improved from a mechanical and physiological standpoint. This is done by the correction of a deviated septum or by subepithelial diathermy cauterization of the inferior turbinates. That the lymphatic system may be the allergic shock organ in infectious mononucleosis is the contention of Pelner and Waldman.[76] All of their patients had a family history of allergy. They contend that a patient with a family history of allergy, presenting fever, adenopathy, and sore throat, should have infectious mononucleosis included in the differential diagnosis. Other laboratory procedures can be done to confirm or deny the specific diagnosis. They found that antihistaminic drugs gave a good degree of improvement prior to other forms of medication. Illustrative case reports have been presented to bring out the salient features of the patients that were seen by them. Aureomycin in the usual dosages effectively aborted the disease in each instance.

The common denominator in six cases of erythema nodosum reported by Roddy[83] was a nonspecific sensitization agent. He reviewed six patients who ranged in age from six to eight years. He concluded that the disease, erythema nodosum, was not a specific one but occurred in sensitized individuals with a variety of sensitizing infectious agents. Within a few days after the administration of sulfonamide medication for an acute sore throat, the patient of Taylor and Jacoby[111] developed facial edema, nausea, and vomiting. This patient presented many hemorrhages into the soft tissues around the face, hematemesis, and complete anuria. The authors did not mention the presence of any familial nor personal history of allergy. At autopsy the adrenal glands were not involved, but the lesions were markedly widespread throughout the kidneys. Another instance of polyarteritis nodosa subsequent to the use of sulfonamide medication is presented by Sinclair and Nitsch.[107] Their patient was a nine-months-old infant with no previous history of allergy, neither personal nor familial. Sulfadiazine had been administered for a period of about twenty-four hours, following which a mild rash was noticed on the abdomen for a duration of about five to seven days. Because of an acute suppurative adenitis, penicillin and sulfadiazine were continued for approximately three weeks. The patient died during laryngoscopy. Subsequent autopsy revealed acute polyarteritis nodosa limited to the coronary arteries. Microscopic involvement was demonstrated in the lungs of patients described by Rose and his coworkers.[85] They have reported upon six patients, one of whom had bronchial asthma and striking eosinophilia of the blood and sputum. Death was due to polyarteritis nodosa. Cardiac changes were present in all of the five patients who died. Only two of these patients presented an eosinophilia of 6 per cent or more. The maximum eosinophilic count was 82 per cent. Abnormal electrocardiograms were obtained in three of the six cases. X-ray evidence of pul-

monary infiltrations characteristic of Loeffler's syndrome was obtained in two patients. Though the lesions of vascular involvement are widespread throughout numerous organs, most cases will show some involvement of the gastrointestinal and genitourinary system. The symptomatology of polyarteritis nodosa is multiple and bizarre, but because of the frequency of involvement in the above two systems most of the complaints can be referred to these areas. Chronic fever, leukocytosis, and the rest of the findings are accompanying features. The classical picture of periarteritis nodosa associated with bronchial asthma and eosinophilia is, according to these authors, uncommon. The multiplicity of symptoms associated with the absence of any evidence of known infectious, parasitic, neoplastic, congenital, or metabolic disease and the presence of involvement of one or more organs should suggest that a diagnosis of periarteritis nodosa be seriously considered. This is the opinion of King[60] who states that biopsy of muscle, nodule, or intra-abdominal organ is the only positive way of making a clinical diagnosis. However, the above associated symptoms and findings should give the physician a definite lead to the diagnosis of periarteritis nodosa.

Because of the lengthy and interesting paper by Brown and Krabek,[9] no attempt will be made in this present review to include the antihistaminic drugs, as they have been surveyed by the various writers during the past year. It is the aim of this reviewer to present in this section some of the more unusual side effects or responses noted with the administration of antihistaminic drugs to various patients. It has been generally accepted that the antihistaminic preparations are of little value in bronchial asthma. Urticaria and seasonal hay fever probably respond in the most acceptable manner to the administration of these agents. Other conditions, however, have been treated with these preparations. Loew[64] believes that spontaneous histaminic cephalalgia and headache induced with injected histamine are diminished in severity by antihistaminic preparations. In general, these drugs have not proven to be of especial value in the relief of pruritus other than pruritus vulvae and pruritus ani. Seyler[98] has shown that there is a definite relationship between at least twelve recently introduced members of this group. He has described chemically four groups of compounds, the first of which includes Benadryl, Decapryn and Hydrillin. The second group includes Pyribenzamine, Neo-Antergan, and Neohetramine. Diatrine, Histadyl or Thenylene, and Chlorathen make up the third group. The miscellaneous group, which includes Trimeton, Antistine, and Thephorin is the fourth of those described by Seyler. It is his impression that when a patient is first given any antihistaminic drug, the physician should prescribe one member of a group. If this is found to be too toxic or conducive to marked side reactions, then a member of another group should be administered rather than repeating essentially the same chemical compound. If relief is obtained from a member of one group but the side reactions are too severe, then the medication should be changed to a less toxic member of the same group. Those members of the fourth or miscellaneous group seem to be particularly useful in the treatment of those patients who usually receive a good degree of sedation from the usual administration of these drugs. Pyribenzamine as a cause of sexual impotence in the male has been described by Jennes.[52] Benadryl did not produce this side reaction, but Thephorin was a causative factor as well as Pyribenzamine. In the first patient, impotence was noticed on the fourth day of Pyrizenzamine therapy which had been prescribed for the relief of urticaria. The impotence was cleared with the discontinuation of the drug, but the urticaria returned in its former degree of severity. Chinn and Oberst[15] could find essentially no difference between the use of Benadryl and Dramamine in the relief of air sickness. They thought that a combination of Hyoscine hydrobromide and Benadryl was more effective than other medication used in their experiments. That the antihistaminic preparations may be of some value in the prevention and treatment of thrombophlebitis migrans has been reported by Selecman and Miller.[97]

Their patients showed very good improvement in venous inflammation within a period of twenty-four hours after the institution of antihistaminic therapy. Other forms of treatment had been without value. Administration of Benadryl and Pyribenzamine has been reported to cause anemia in three patients of Crumbley.[24] After the use of these preparations varying from two months to fourteen months, three patients with anemia failed to respond to the use of liver and iron. However, the blood picture returned to normal in each of the three cases upon the withdrawal of the antihistaminic drug. That this production of anemia is a rather unusual side effect in the use of antihistaminic preparations is established by the absence of similar reports in the literature. There have been publications in which the use of antihistaminic drugs has been continued for many months with no consequential change in the blood picture. Pyribenzamine has been reported to produce agranulocytosis. Hilker[45] describes a patient whose white blood count was 1,700 after a period of seven weeks with Pyribenzamine therapy. Inasmuch as no other medications had been used during this interval and the blood picture returned to normal with the withdrawal of the Pyribenzamine, the point was established that the antihistaminic drug probably was the causative factor. Martland and Guck[65] report a similar instance of agranulocytosis following the use of Pyribenzamine. Their patient experienced almost immediate symptoms of malaise, abdominal cramping, and headache following the first few dosages of the preparation. However, treatment was continued and the patient eventually was found to have a leukopenia with almost complete absence of the granulocytes. The blood picture returned to normal with the withdrawal of Pyribenzamine and the use of supportive measures. Another trial on Pyribenzamine resulted in the initiation of a similar picture in that there was a progressive decrease in the white blood cells but not an established granulocytopenia. These accounts of unusual reactions to the use of Pyribenzamine bring to mind a patient seen by this reviewer approximately two or three years ago. The patient was complaining of acute symptoms of seasonal hay fever but had never had antihistaminic agents prescribed for her. She was supplied with a few tablets of Pyribenzamine with the instructions to use one tablet every four hours. Within ten or fifteen minutes following the administration of the first tablet, the patient became somewhat alarmed because of a rather marked pain in her chest. This chest pain could not be localized and seemed to be aggravated by a prone position. Thirty minutes after the onset of the chest pain, the patient was delirious, loud, disoriented, and agitated. Her symptoms of seasonal hay fever definitely were of secondary importance at this point. The patient was hospitalized, where sedation seemed to give her some relief from the chest pain as well as to quiet the general picture. Twelve hours after hospitalization the patient had returned to normal but did not remember any of the details of her excursion. The accidental ingestion of a quantity of Benadryl by a two-year-old child has been reported by Davis and Hunt.[25] Drowsiness, convulsions, cyanosis, and elevated temperature were followed within a period of twelve to fifteen hours by coma. Death occurred with the most important pathological findings being pulmonary congestion, passive congestion in the liver and kidneys, and petechial hemorrhages in the brain.

The recent advantages ascribed to the use of antihistaminic drugs for the treatment of acute colds have not been proven by the work of Hoagland et al.[48] In a controlled study, 190 patients were investigated. Sixteen per cent of this number reported "cures" within twenty-four hours from oral antihistaminic preparations. Twenty-seven per cent of seventy patients who had received placebos also reported "cures." Antihistaminic drugs—Pyribenzamine and Tagathen—were given orally and by nebulizer. Those patients receiving the antihistaminic drugs did note a decrease in the amount of nasal discharge as compared to that reported by the patients receiving placebos. The authors have concluded that antihistaminic drugs, both by

mouth and by nebulizer, may decrease nasal discharge, but the remaining points of the illness were not appreciably affected.

In a very clear explanation of the usefulness and limitations of cortisone and ACTH, Hench[43] has stated that these preparations appear to have little or no effect upon the irritant but seem to provide a buffer to the susceptible tissues. The manner in which these hormonal agents produce their effect is so far unknown. Their influence is exerted upon the disease and not upon the etiologic factor of any condition in which it is used. Carryer et al[13] found that each patient received prompt relief from the symptoms of asthma and hay fever with the use of Cortisone. The relief was greater than had been obtained by any previous form of medication. Complete relief was experienced in their patients within a period of three days following the institution of the medication. They did not notice any unpleasant symptoms occurring as the result of the use of the hormone. The use of cortisone and ACTH in periarteritis nodosa and cranial arteritis has been reported by Shick and his coworkers.[104] Cortisone was administered to four patients with periarteritis nodosa, and two others were treated with ACTH. All the patients received prompt and almost dramatic relief within twenty-four to seventy-two hours after the institution of treatment. The improvement was considered, however, to be only a clinical remission. The impression was gained that the agents must be given early in order to prevent any widespread vesicular damage. As in other diseases in which these agents have been found beneficial, the feeling persists that the complaints have not been "cured" because the causative substance of the symptoms has not been eradicated but only interrupted. Good relief in five patients with bronchial asthma was noted on ACTH therapy by Bordley and his co-workers.[8] The initial dose for each patient varied from 30 to 100 mg, with the individual dosages being given at intervals of every six hours. Treatment was continued for as long as twenty-one days, with a gradual reduction in therapy after recovery was noted. Only one patient remained asymptomatic for as long as one month after treatment was discontinued. Nasal polyps were also found to shrink under this therapy. These authors report a diminution in the response to skin test while on ACTH therapy, but the former level returned when the medication was discontinued. In contrast to this is the review by Brown[10] who has stated that most skin reactions have been in no way changed by ACTH therapy. Rose et al [84] have suggested that the activity of ACTH in bronchial asthma patients may be due to the restoration of the histidine-histamine balance in the lungs. Six patients were treated by these authors. Four of the patients experienced almost complete relief for a period of one month or less. Two weeks following the cessation of therapy, the symptoms returned in their former degree of severity. The skin tests in their patients were not affected by the hormone. No gross changes in skin tests could be determined by Zeller, Randolph, and Rollins.[121] Their patients were seen during the 1949 ragweed season. Treatment with ACTH was instituted, following which serial dilutions of ragweed extract were applied to the arm. No changes were noted in the degree of skin test reaction to the pollen extract. Histologic studies revealed prominent eosinophilic infiltration and edema in wheals that had been biopsied. These wheals had been produced by the ragweed extract injected intradermally. However, following ACTH therapy, there was a definite reduction in the number of eosinophils and an increase in polymorphonuclear cells. Similar changes were noted in the blood. Passive transfer sites were not influenced by hormonal therapy. Randolph and Rollins[80] could not observe any undesirable side effects from the administration of ACTH in short intensive courses. There were relatively long periods of rest between each course for each patient. The dosage schedule used in these patients was 25 mg every six hours. A reduction in dosage was indicated with clinical improvement. No other symptomatic therapy was required for a period of two to three weeks in any of the patients on ACTH treatment. Results in ragweed hay fever were almost startling, inasmuch as the patients were relieved after a short

intensive course for the remainder of the season. The dosage required for the hay fever patients varied from 125 to 225 mg of ACTH in divided doses. Improvement was noted within a matter of hours after the institution of therapy. These same authors[81] report a patient with gastrointestinal allergy who remained free of any symptoms for a period of two weeks following hormone treatment. This was noted even though the diet included those foods that had been the chief causes of her allergic symptoms. When hormone therapy was first introduced for bronchial asthma, it was the impression of many men practicing allergy that the solution to their problems—and their practice!—had been found. Burrage,[11] in a review of the early reports of ACTH and cortisone in allergic conditions, has tended to refute these optimistic opinions. Though the fundamental processes by which these hormonal agents affect the allergic diseases is unknown, the results are sometimes dramatic. Complications of their use, however, may be dangerous. This reviewer recalls one patient who had been on ACTH therapy with dramatic response for her very severe symptoms of intractable bronchial asthma. She remained symptom free for approximately three weeks, when a recurrence of symptoms in their former severity necessitated a resumption of ACTH therapy. Therapeutic response was again satisfactory but the remission was not as prolonged as that following the original course. Subsequently, a maintenance dosage was established. The patient did quite well for approximately three weeks, when the severity of her asthmatic symptoms was noticed to be increasing regardless of the increase in dosage and frequency with which the ACTH was administered. Though all laboratory findings were well within normal limits and ranges, the patient continued in extreme asthma (?) and eventually lapsed into a coma and expired. Permission for autopsy could not be obtained, so it must, therefore, be assumed that ACTH did play some part in producing this fatality. Thorn and his co-workers[113] believed that ACTH and cortisone are effective drugs in asthma when any ordinary medication proves to be a failure. They are in agreement with most of the other reports that the relief experienced by the asthmatic patient under ACTH therapy is temporary at best, and, as a rule, prolonged remissions may be possible but are not always found. Herbert, deVries, and Rose[44] found that the administration of ACTH usually resulted in a transient leukocytosis as well as a decrease in the percentage of circulating eosinophils. In one of their patients with an eosinophilia of 98 per cent, the cells practically disappeared from the peripheral blood stream under the influence of ACTH. Many of the findings originally observed in laboratory animals treated with ACTH have not been substantiated in humans. They performed blood histamine studies upon their patients and felt that these findings did corroborate their opinion that the eosinophil is not responsible for the transportation of histamine. Most of the reports on the use of ACTH and cortisone at the present time have been case reports, with the general agreement that response to this form of treatment is very satisfactory in most allergic states. The improvement, however, is only temporary and repeated courses of therapy are usually indicated. The question at the present time concerns the advisability of repeated courses of hormonal therapy producing changes other than those anticipated. The attention of the reader is directed to the colorful and interesting scientific exhibit of Carlisle, Gibson, and Schmatolla[12] demonstrating the chemistry, effect and results of the use of cortisone.

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FOLIC ACID AND HISTAMINE

(Continued from Page 229)

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In Memoriam

RETLA H. ALTER

It is with extreme regret that we announce the death of Dr. Retla H. Alter, Fellow of The American College of Allergists since its inception. Dr. Alter was also a member of The American Academy of Allergy. He was a practicing physician at Jackson, Michigan, for over twenty-five years. He collapsed from a heart attack, February 14, soon after making a call at the home of a patient. He had just returned from the annual meeting of the College in Chicago.

Dr. Alter was born in Rushville, Indiana, July 22, 1896. After receiving his basic education in the Rush County schools, and graduating from high school in Moscow, Indiana, in 1914, he attended the University of Michigan, receiving his B.S. degree in 1920. He was graduated from the University of Michigan Medical School in 1925 and interned at Foote Hospital for one year before starting practice in Jackson, Michigan. Dr. Alter did much postgraduate work, including study at the New York Postgraduate School in 1944 and at Columbia University in 1945.

He was a member of the Jackson County Medical Society, which he served as president in 1940 and also as secretary in an earlier year; the Jackson Academy of Medicine and Dentistry, of which he was secretary from 1941 to 1947; the Michigan State Medical Society; the American Medical Association; the International Correspondence Club of Allergy; the Michigan Allergy Society; and the Aeromedical Association.

Dr. Alter was a member of the Foote Hospital board, serving since 1944; a member of staffs of both Foote and Mercy Hospitals; and was Chief of the Foote Hospital staff in 1941. He was a past president of the Jackson University of Michigan Alumni Club. He was a member of the Masonic Order.

Surviving are his widow, Mrs. Vivian Vanderlyn Alter, whom he married in 1935; a daughter by a previous marriage, Mrs. Orville Aten; and two grandsons, David and Dennis Aten, all of Jackson; his parents, Mr. and Mrs. D. O. Alter, and a sister, Mrs. Bert Reed, of Rushville; and two brothers, Dr. Wayne Alter, St. Paul, Indiana, and Dr. Chester Alter of Boston, Massachusetts.

The officers of the College and all members join in extending their sincere sympathy to the family for the sudden loss of a man cut short in the prime of life when carrying on his faithful duties.

JOHN DECARLO

We are very sorry to announce the death of Dr. John DeCarlo, 1629 South Broad Street, Philadelphia 48, Pennsylvania, on December 12, 1950. Dr. DeCarlo had been an Associate Fellow in the College since 1946.

Dr. DeCarlo was born in Italy, January 5, 1888. He was graduated from Central High School in Philadelphia, and from Jefferson Medical College in 1911. He interned at Chester County Hospital the following year and took a postgraduate course in gastroenterology at Massachusetts General Hospital. He held the position of Associate in applied and topographic anatomy at the Jefferson Medical College until a few years ago. He was Medical Chief of St. Agnes Hospital in Philadelphia, and he served in the Outpatient Department of Jefferson Medical College Hospital. He was very much interested in gastroenterology and its allergic manifestations.

He was a member of the American Anatomical Society, the American Association for the Advancement of Science, the Philadelphia Allergy Society, the Philadelphia Medical Society, the Pennsylvania State Medical Society, and the American Medical Association. He was chairman of the South Branch of the Philadelphia County Medical Society.

The College deeply mourns his loss and extends its sincerest sympathy to members of the family.

FIRST INTERNATIONAL CONGRESS OF ALLERGISTS

Zurich, September 23-29, 1951

Organized by the International Association of Allergists, Inc.

Travel Arrangements for the Congress

The American Express has been appointed Official Transportation Agent to handle travel arrangements for those from the United States who will attend the First International Congress of Allergists. Reservations may be requested through your travel agent, according to the tear-out sheet below.

Eastbound sailing dates on the *Ile de France* and the *Queen Elizabeth* are August 29 and September 14. Westbound sailing dates on the *Liberte* and the *Queen Elizabeth* are October 5 and October 23. Since steamship and hotel accommodations are limited, it is imperative that reservations be made as soon as possible.

Both members of I.A.A. and nonmembers are invited to attend. Those wishing to attend the Congress without participating in any official tour may obtain individual itineraries upon request.

Tour No. 1, forty-four days visiting France, Italy, Switzerland, Belgium, and England, is a pre-Congress tour leaving New York, August 29, and returning October 11. Tour No. 2 is a post-Congress tour of forty-five days visiting France Switzerland, Italy, Belgium, and England, leaving New York, September 14 and returning October 28.

Prices per person are as follows:

Tour No. 1

Including Minimum First Class Steamship Round Trip	$1347.00
Including Minimum Cabin Class Steamship Round Trip	1122.00
*Including Minimum Tourist Class Steamship Round Trip	1017.00
Including Round Trip Trans-Atlantic Air Transportation	1385.00

Tour No. 2

Including Minimum First Class Steamship Round Trip	$1576.00
Including Minimum Cabin Class Steamship Round Trip	1294.00
*Including Minimum Tourist Class Steamship Round Trip	1171.00
Including Round Trip Trans-Atlantic Air Transportation	1441.00

*NOTE: Passengers desiring accommodations in tourist class should register request. Every effort will be made to secure such accommodations.

A deposit of $150 is required to protect your reservation. On cancellation four weeks prior to departure, the deposit will be refunded in full. On cancellation less than four weeks prior to departure, the deposit will be refunded in full less any fee assessed by the steamship company.

Write the American Express Company for a preliminary program and a travel brochure which gives full details about meals, accommodations, and sightseeing.

REQUESTS FOR RESERVATIONS

TO: American Express Company
65 Broadway
New York 6, New York

OR

TO: Your Travel Agent

I wish to apply for membership in the First International Congress of Allergists, Tour No....., and I desire Trans-Atlantic reservations as follows:

First Class on Steamer ☐ Tourist Class on Steamer ☐

Cabin Class on Steamer ☐ Round Trip by Air ☐

I desire hotel reservations in Zurich on the basis of:

De Luxe ☐ Double Room ☐

First Class ☐ Single Room ☐

Second Class ☐

Third Class ☐ Without Bath ☐

Pension ☐ With Bath ☐

Congress Card desired: "M" for Congress Members ☐

"AM" for Associate Members ☐

INDEPENDENT ARRANGEMENTS

Instead of participating in one of the Escorted Tours, I desire to travel independently and would like to obtain Trans-Atlantic reservations as follows:

By steamer: First Class ☐ Cabin Class ☐ Tourist Class ☐

By Air: ☐

I am also interested in taking a European Tour

of about.....days

☐ Before the Congress, visiting the following countries:

☐ After .....

NAME .....

ADDRESS .....

.....

Names and addresses of other persons in my party.

NAME .....

.....

.....

News Items

NEW YORK ALLERGY SOCIETY AWARD

The New York Allergy Society announces a prize of $150.00 for the best essay of merit on a subject in immunology or clinical allergy. Competition is open to students of the medical schools of New York City. The essay ought not to exceed 15,000 words.

All papers must be sent to the Secretary of the New York Allergy Society, Dr. Frederick R. Brown, 145 East 52nd Street, New York 22, New York, prior to October 1, 1951.

SOUTHEASTERN ALLERGY ASSOCIATION

At a meeting of the Southeastern Allergy Association in St. Petersburg, Florida, January 20 and 21, the following officers were elected:

President: L. C. Todd, M.D., F.A.C.A., Charlotte, North Carolina
President-elect: Clarence Thomas, M.D., Nashville, Tennessee
1st Vice President: Frederick Hieber, M.D., F.A.C.A., St. Petersburg, Florida
2nd Vice President: Lindsay Miller, M.D., F.A.C.A., Gadsden, Alabama
Executive Committeemen:
Raymond Arp, M.D., Associate, A.C.A., Atlanta, Georgia
Charles Wofford, M.D., F.A.C.A., Johnson City, Tennessee
Secretary-Treasurer: Katherine MacInnis, M.D., F.A.C.A., Columbia, South Carolina

Harold Abramson, M.D., President of The American College of Allergists, was guest speaker at the meeting.

Dr. L. C. Todd's new address is Suite 3A, Doctors' Building, 1012 King's Drive, Charlotte, North Carolina.

NATIONAL HOME FOR JEWISH CHILDREN AT DENVER

In April, 1930, the *American Journal of Diseases of Children* published an article by M. Murray Peshkin, M.D., F.A.C.A., Chief of the Children's Allergy Clinic of Mt. Sinai Hospital in New York City, entitled "Asthma in Children—A Plea for a 'Home' as a Restorative Measure."

In 1940, Dr. Peshkin was informed that the National Home for Jewish Children at Denver had undertaken the long-range care of asthmatic children. After two generations of service to children of the tuberculous poor, the directors of the Home had extended its ideal facilities to include the care of children suffering from chronic asthma who were not responding to the accepted standards of modern medical treatment in their own communities.

This physical and mental hygiene program for the rehabilitation of asthmatic children and those suffering from other allergic disorders, is the only one of its kind in the country. The Home has facilities for 140 children, of whom 85 per cent fall in this category. They come from all over the country through referrals from physicians, family social service agencies, and private sources. It is a non-profit organization, supported by private philanthropy and making no charge for its extraordinary service.

The average stay at the Home is approximately two years. In its After-Care Clinic for children residing in the Greater New York area, a periodic re-examination of the discharged children is made to determine the benefits they derived at the Home. At this time, 82 per cent of the children are completely relieved

of their asthma or have only an occasional spell of it, after one or more years of residence in their respective homes.

In many of the cases it is essential that the teamwork of the physician, the psychiatrist, and the case worker be employed for the successful treatment of the whole child, for we are concerned with an emotionally disturbed child from a psychologically harmful environment whose disturbance is superimposed on a chronic allergic condition.

One of the latest features to be added to the Home is a completely air-conditioned building, equipped with air filtration and radiant heating, for the housing of the more difficult asthmatic cases. It is the only building of its kind in America.

Application may be made by getting in touch with the New York office of the Home at 1407 Broadway, New York 18, New York, or the Los Angeles office, 3932 Wilshire Boulevard, Los Angeles, California, or by writing directly to the Home at 3447 West 19th Avenue, Denver 4, Colorado.

PRACTICE AVAILABLE

Mrs. R. H. Alter, widow of the late Dr. R. H. Alter, a Fellow of the College whose obituary appears in this issue, writes that there is an excellent opportunity for an allergist to take over Dr. Alter's extensive practice. Those interested may write directly to her at 801 S. West, Jackson, Michigan.

RAGWEED POLLINOSIS (HAY FEVER)—A PUBLIC HEALTH PROBLEM IN SCHOOL CHILDREN

(Continued from Page 228)

CONCLUSIONS

A survey of 2,140 children was made in the city of Rochester, New York, to determine the incidence of ragweed pollinosis (hay fever) during the first two weeks of the school year 1948-1949. One hundred seventy eight (8.3 per cent) had suffered from ragweed pollinosis. In sixty-seven (3.1 per cent), this was complicated by asthma. In thirteen instances (0.6 per cent), the patients left Rochester for areas of low pollen count. The authors feel that this constitutes a public health problem of considerable importance and that a detailed larger survey, particularly of high school students, is indicated. This would be even more desirable in those areas in New York State and others states where school is customarily opened immediately after Labor Day, and where the ragweed pollen index is in excess of that in Rochester.

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300 South Goodman Street

BOOK REVIEWS

PSYCHOSOMATIC MEDICINE—Its Principles and Applications. By Franz Alexander, M.D. Price $4.00. New York: W. W. Norton and Company, Inc., 1950.

Any book by the noted psychiatrist, Franz Alexander, is welcome. This volume is no exception to the rule. It answers the need for a basic presentation of the psychosomatic approach in medicine. Dr. Alexander sets forth two objectives: to describe the fundamental concepts on which this approach is based, and to present the results of study concerning the influence of emotions on bodily processes in health and disease. His book draws a clear picture of the psychological factors involved in a body process and shows that these factors must receive the same detailed scrutiny as would the physiological processes.

In many chronic diseases, therapeutic possibilities have been established. Dr. Alexander devotes chapters to the discussion of emotional factors in gastrointestinal disturbances, including stomach neuroses, peptic ulcers, and colitis; respiratory disturbances such as bronchial asthma; cardiovascular disturbances including essential hypertension, vasodepressor syncope, and migraine; to emotional factors in skin diseases, in endocrine disturbances, and in rheumatoid arthritis and other conditions of the joints and muscles. Disturbances of the sexual functions are discussed in a chapter contributed by Dr. Therese Benedek.

The reviewer believes that the detailed scrutiny of psychological factors requires more verbatim recordings of psychotherapeutic interviews. The next step in the scientific construction of scientific psychotherapy will involve the assembly and arrangement of psychosomatic data which should be available as are other data of science.

THE DIFFERENTIATION OF ESCHERICHIA AND KLEBSIELLA TYPES. By F. Kauffmann, M.D., Chief, International Salmonella Center, State Serum Institute, Copenhagen, Denmark. 57 pp. Price $2.00. (American Lecture Series, No. 84.) Springfield, Ill: Charles C Thomas, 1951.

The techniques for the classification of Salmonellae by serological techniques (in whose development the author took a prominent part) were in recent years extended to the Gram-negative bacilli commonly known as colon and Friedlander groups. This work was largely done in Kauffmann's laboratory. In the present monograph the methods are concisely described and the results are summarized and tabulated. Generic differentiation is obtained by cultural characteristics and subdivision into types by determination of antigen, particularly of the (heat stabile) somatic or O antigens and of the heat stabile or heat labile, capsular or envelope antigens "K." The report is restricted entirely to the work done in the Copenhagen Laboratory; it does not consider—in fact, does not even mention—the data collected and the classifications arrived at elsewhere.

As to the application of these observations to clinical medicine, it is of great interest to note that relatively few types were found to cover the great majority of strains investigated. This is also true of strains derived from pathological material. To the allergist each increment in knowledge of the antigenic composition of bacteria from human sources—regardless of whether pathogenic or commensal—is of interest, because these data form the base on which eventually exact information on the relationship of microörganisms to hypersensitivity will be obtained.

VERNAL CONJUNCTIVITIS. By M. N. Beigelman, M.D., Los Angeles, California. 430 pages. Los Angeles: University of Southern California Press, 1950.

This monograph on the subject of vernal conjunctivitis represents a very extensive and comprehensive review of the literature. This disease has been known for many centuries and yet some phases of it remain unsolved.

It is noteworthy that Dr. Beigelman made a histopathological study of thirty-six cases. The historical, clinical, and therapeutic aspects of the disease have been thoroughly covered.

The chapter on histopathology is especially outstanding. Here the author discusses the changes in the epithelium and the cellular infiltration of the substantia propria, as well as other corneal involvements. He correlates these findings with the clinical observations.

The Symposium on Etiology is very well done. The manner in which he deals with the allergic aspect of the disease and his conclusions are those which are generally accepted today. The following statement appears particularly significant: "Finally, the combined results of clinical observations, laboratory tests, experimental studies, and therapeutic trials have formed a solid basis for the assumption that in vernal conjunctivitis we are dealing with a specifically hypersensitive person. Less decisive and binding are the evidences submitted to establish the purely allergic nature of the disease. But these evidences are so important—one might say so overwhelming—that hypersensitiveness, mainly to material substances, must be considered as the most promising working hypothesis."

In the chapter on therapy, the discussion considers treatment by the application of copper, silver, mercury, and zinc. There is also discussion on the use of salicylates, neutral red therapy, vasodilators, vasoconstrictors, antihistaminic drugs, and caustic acids. The author refers to some of the work done in the Scandinavian countries, such as the application of cold and freezing with carbon dioxide. Such methods, however, have been generally discarded. He also discusses the application of heat by actual cautery, diathermy, and electrolysis, and finally, local x-ray and radium therapy.

Furthermore, he reviews the results of surgical treatment, the use of foreign proteins, the removal of foci of infection, and endocrine therapy. Consideration of the use of allergens in the treatment is mentioned only briefly.

A review of the complete volume should be informative to those interested.

BOOK ANNOUNCEMENTS

The American Association for the Advancement of Science announces two new volumes, published in January, 1951. One, entitled *Pituitary-Adrenal Function,* includes twenty-two papers delivered at a two-day Symposium on the Adrenal Cortex at the AAAS meeting in New York City, December, 1949. The table of contents lists twenty-three topics, assembling important contributions on the regulation of adrenal cortical activity, the role of the cortical hormones in protein, carbohydrate, and mineral metabolism, and effects of the cortical steroids and ACTH in various disease states. Clothbound, illustrated, 220 pages, 6 x 9 inches, $3.50.

The other volume is the *AAAS Proceedings and Directory, 1940-1948,* and *Centenary Supplement.* The first volume contains 40,000 names and biographical sketch of members; the second volume includes the 13,000 scientists who joined the AAAS in 1948. Clothbound, 1218 pages, 6 x 9 inches, both volumes on one order, $8.50.

The AAAS also announces a reprinting of *Brucellosis,* a symposium sponsored

by the National Institutes of Health, the U. S. Department of Agriculture, and the National Research Council. This volume, published in July, 1950, was out of print before the end of the year. Clothbound, illustrated, 277 pages, 6 x 9 inches, $3.50.

* * *

The Chemical-Biological Co-ordination Center of the National Research Council has announced the publication of the third volume in its series of reviews concerned with chemical structure-biological activity relationships.

CBCC Review No. 3, *Histamine Antagonists* (122 pages, $1.50) by Drs. Frederick Leonard and Charles P. Huttrer, discusses the pharmacological properties, methods of *in vitro* and *in vivo* evaluation, methods of synthesis, structure-activity relationships, mechanism of action and clinical application of histamine antagonists. More than 1000 compounds which have been tested for potential antihistaminic activity are listed in forty-eight classified tables including structures, activities, and references to the literature. Emphasis is placed on the analysis of structure-activity correlations within the different classes of compounds, and on generalizations which can be deduced. The review contains 224 references.

Copies may be obtained from the Publications Office, National Academy of Sciences, 2101 Constitution Avenue, N. W., Washington 25, D. C.

* * *

The International Association of Allergists announces two new volumes, one in English and one in German. *Progress in Allergy,* Volume II, edited by Paul Kallós of Helsingborg, Sweden, contains chapters from the following contributors: H. A. Abramson, F.A.C.A., New York; K. Bucher, Basel, Switzerland; Robert A. Cooke, F.A.C.A., New York; French K. Hansel, F.A.C.A., St. Louis; H. Haxthausen, Copenhagen; Hjalmar Koch, Stockholm; F. A. Simon, F.A.C.A., Louisville; George L. Waldbott, F.A.C.A., Detroit; and Fred W. Wittich, F.A.C.A., Minneapolis. Clothbound, 50 figures, 37 tables, 356 pages, $7.50. The publisher is S. Karger, Basel; agent for the western hemisphere is Interscience Publishers, Inc., New York.

The volume published in German is entitled *Fortschritte der Allergielehre.* It is also edited by Paul Kallós, and outstanding contributors are G. Dahlberg, Uppsala; G. Dohlman, Lund; A. Grumbach, Zurich; D. Harley, London; F. Haurowitz, Istanbul; S. Hellerstrom, Stockholm; K. Jaffé, London; R. Kaijser, Uppsala; L. Kallós-Deffner, Stockholm; and R. Wagner, Boston. Clothbound, 38 figures, 400 pages, $7.50. The publisher is S. Karger; agent for the U.S.A. is Nordeman Publishing Company, Inc., 215 Fourth Avenue, New York.

Both volumes may be ordered directly from The International Association of Allergists, 424 LaSalle Medical Building, Minneapolis 2, Minnesota.

THE EFFECT OF ANTIHISTAMINE MEDICATION ON THE TUBERCULIN REACTION IN ADULTS

(Continued from Page 207)

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9. Sarber, R. W.: Effect of Benadryl hydrochloride on the tuberculin reaction in guinea pigs. Am. Rev. Tuberc., 57:504, 1948.

(Dr. Oliveira Lima)
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